

Palladium-Catalyzed Functionalization of Olefins and Alkynes: From Oxyalkynylation to Tethered Dynamic Kinetic Asymmetric Transformations (DYKAT)

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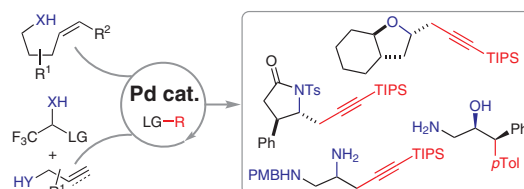
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Abstract This review presents an account of the palladium-catalyzed functionalizations of alkenes and alkynes developed at the Laboratory of Catalysis and Organic Synthesis (LCSO). Starting from the intramolecular oxy- and aminoalkynylation of alkenes, tethered methods were then developed to functionalize allylic amines and alcohols, as well as propargylic amines. Finally, a new dynamic kinetic asymmetric transformation was developed based on the use of a ‘one-arm’ Trost-type ligand, giving access to enantiopure amino alcohols. Each section is a personal account by the researcher(s) who performed the work.

- 1 Introduction,
- 2 Oxy- and Aminoalkynylation of Olefins,
- 3 In Situ Tethering Strategies for the Synthesis of Vicinal Amino Alcohols and Diamines,
- 4 Carboamination of Allylic Alcohols,
- 5 Carboxygenation of Propargylic Amines,
- 6 Enantioselective Carboetherification/Hydrogenation via a Catalytically Formed Chiral Auxiliary,
- 7 Conclusion

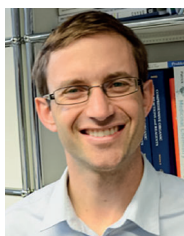
Key words synthetic methods, palladium catalysis, alkynes, Trost ligands, DYKAT

1 Introduction (Jerome Waser)

Palladium catalysts have been extremely successful in synthetic chemistry.¹ This has been recognized by the award in 2010 of the Nobel Prize in Chemistry to Heck, Negishi, and Suzuki for the development of palladium-cata-

lyzed cross-coupling reactions. In 2006, I was a postdoctoral scholar in the Trost group, and although my personal project involved ruthenium catalysis and total synthesis, palladium catalysis was intensively investigated by other group members. In particular, new asymmetric transformations involving either ‘triple A’ (Asymmetric Allylic Alkylation)² or ‘TMM’ (trimethylenemethane)³ chemistry were flourishing. The use of palladium catalysis to develop new transformations in organic synthesis was therefore very attractive to me, but I obviously did not want to remain in the same lines of research as the Trost group. At that time, I particularly admired the impressive work of the Sanford group on high-oxidation-state palladium catalysis, often using hypervalent iodine reagents.⁴ I wondered if such reagents could be used to diverge the well-known palladium-catalyzed Wacker cyclization away from the conventional β -hydride elimination (Scheme 1, Path **a**) process to give more functionalized products (Scheme 1, Path **b**). A fast oxidation from a Pd(II) intermediate **I** to a Pd(IV) complex **II**, followed by reductive elimination would indeed change the usual reaction pathway. As one of my main research goals was to develop new alkyne chemistry, the use of alkynylidonium salts appeared especially interesting, taking into account the report by Canty and co-workers on the stoichiometric oxidative alkynylation of a Pd(II) complex using such reagents.⁵ The model system that I drew in my initial research proposal in 2006 was based on a successful Wacker cyclization process reported by Stoltz and co-workers involving phenols as nucleophiles.⁶

Biographical Sketches



Jérôme Waser was born in Sierre, Valais, Switzerland, in 1977. He obtained his chemistry diploma at ETH Zurich in 2001. From 2002 to 2006, he was a Ph.D. student at ETH Zurich with Professor Erick M. Carreira. He then joined

Professor Barry M. Trost at Stanford University as an SNF postdoctoral fellow. From 2007 to 2014, he was an assistant professor at EPF Lausanne (EPFL). Since June 2014, he has been an associate professor at EPFL. He is a recipi-

ent of the ERC Starting Grant (2013) and Consolidator Grant (2017), the Werner prize of the Swiss Chemical Society (2014), and the Springer Heterocyclic Chemistry Award (2016).



Stefano Nicolai was born in Civitavecchia (metropolitan area of Rome), Italy, in 1979. He obtained his bachelor's and master's degrees at the Sapienza, University of Rome, in 2005 and 2007, respectively. From 2009 to 2013, he was

a Ph.D. student at the Ecole Polytechnique Fédérale de Lausanne, under the supervision of Professor Jérôme Waser. From 2014 to 2015, he worked in the New Synthetic Ingredients Discovery division at Firmenich (Geneva) as a

postdoctoral scientist. He rejoined Professor Waser's research group at the EPFL in late 2015, and is currently working as an *Associé à la Recherche* (research scientist).



Ugo Orcel was born in Annecy (France) in 1989. He graduated from the Ecole Nationale Supérieure de Chimie de Montpellier (France) in 2012. He completed his Ph.D. at the Ecole Polytechnique Fédérale de Lausanne

(Switzerland) in 2017, under the supervision of Professor Jérôme Waser. He then joined the group of Professor Bernhard Breit at the Albert-Ludwigs-Universität Freiburg (Germany) to pursue his postdoctoral studies with an Early

Postdoctoral Mobility Fellowship of the SNSF. Since 2018, he has worked for F. Hoffmann-La Roche in Basel (Switzerland) in process chemistry.



Bastian Muriel was born in Neuilly-sur-Marne, France, in 1992. He received his bachelor's degree in organic chemistry from the University of Bordeaux in 2014. In 2016, he joined the LCSO

group for his master's thesis, working on the palladium-catalyzed difunctionalization of alkenes. He obtained his master's degree in 2016 from the University of Bordeaux, and then returned

to Lausanne for his doctoral studies under the supervision of Professor Waser. His current research interests lie in the development of new radical-based methodologies exploiting ring strain.



Phillip Greenwood was born in West Sussex, UK, in 1991. He received his master's degree from Imperial College London in 2015. He then joined the

LCSO group in 2015 to carry out his Ph.D. studies under the supervision of Professor Jérôme Waser, with funding from the SNF and ERC to carry out teth-

ering reactions with palladium catalysis. Graduating from EPFL in 2020, he currently works at Pfizer, Sandwich, as a process development chemist.



Luca Buzzetti was born in Morbegno, Italy, in 1990. He studied chemistry at the University of Pavia, where he obtained his bachelor's (2012) and master's (2014) degrees. From 2014 to 2018, he was a Ph.D. student under the

supervision of Professor Paolo Melchiorre at the Institute of Chemical Research of Catalonia (ICIQ, Spain), where he worked on the development of enantioselective photochemical reactions. Since 2019, he has been a

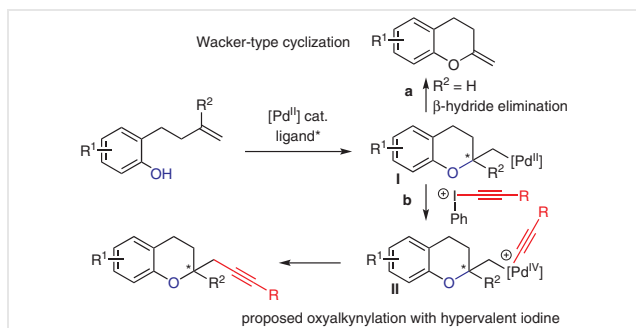
postdoctoral researcher in the group of Professor Jérôme Waser at EPFL (Lausanne), and he is currently investigating asymmetric transition-metal-catalyzed reactions.



Mikus Puriņš was born in Riga, Latvia, in 1994. He received bachelor's (2017) and master's (2019) degrees in chemistry at Riga Technical University under the supervision of Professor Māris

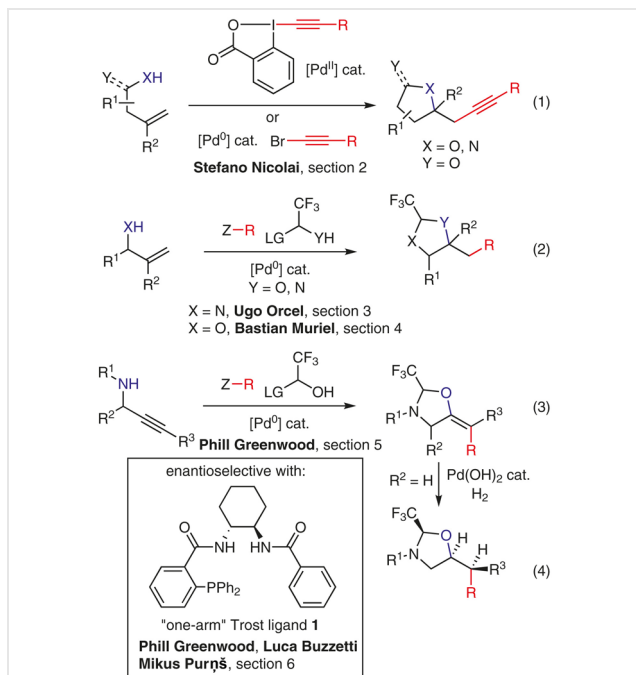
Turks. Currently, he is pursuing his doctoral degree under the supervision of Professor Jérôme Waser at the Swiss Federal Institute of Technology, Lausanne (EPFL), Switzerland. His current

research interests include tethering strategies for selective functionalization of small molecules.



Scheme 1 Original research proposal: from Wacker-type cyclization to oxyalkynylation (October 2006)

The implementation of this plan started in our group in 2008, with the master's project of Stéphane Erard. The product was indeed obtained, but only in low yield. It was finally thanks to Stefano Nicolai, who started his Ph.D. studies in January 2009, that the project could be brought to completion (Scheme 2, eq. 1).⁷ In section 2, he will tell this story, and also how he developed, in addition an aminoalkynylation process,⁸ a second catalytic system based on Pd(O)/Pd(II).⁹



Scheme 2 Research in palladium-catalyzed functionalization of alkenes and alkynes performed at LCSO from 2009 to 2020

The work of Stefano represented an important breakthrough, but was still based on the intramolecular reaction of a nucleophile with the alkene. When Ugo Orcel joined the group in 2012, I therefore proposed that he should de-

velop intermolecular reactions. This was a struggle that was ultimately unsuccessful. Nevertheless, Ugo did not give up and finally developed an in situ tethering methodology for the carboxygenation and carboamination of allylic amines (Scheme 2, eq. 2).¹⁰ This general approach was not only useful for alkynylation, but could be also extended to arylation. In section 3, Ugo will explain how he came to this elegant solution.

The approach was not limited to allyl amines; Bastian Muriel extended it to allyl alcohols during his master's work under the supervision of Ugo (Scheme 2, eq. 2).¹¹ Again, this was not as easy as expected, and new ligands had to be developed (section 4).

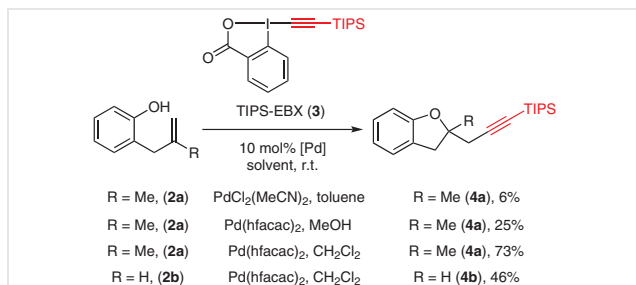
When Phillip D. G. Greenwood joined the group in 2015, he received the task of further addressing the limitations of the tether methodology: in particular, it could be used only for the formation of five-membered ring and with terminal olefins. Overcoming these limitations was important for application of the method in total synthesis. After the usual first year of 'fishing', Phill was finally able to extend the method to the carboxygenation of alkynes (Scheme 2, eq. 3).¹² In contrast to alkenes, substituents were tolerated and tetrasubstituted olefins were obtained with high stereoselectivity. More about that can be found in section 5.

Finally, the last chapter of this story was also started by Phill: our first realization of an enantioselective transformation. Indeed, Phill observed that the tetrasubstituted olefins generated by his method could be hydrogenated with complete diastereoselectivity (Scheme 2, eq. 4). It would be 'sufficient' to develop an enantioselective route to the oxazolidine to have access to optically pure amino alcohol derivatives. But to realize this goal, an unprecedented palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT; a concept well-known in the Trost group) had to be developed. This was extremely challenging, and required the work of an exceptional team composed of Phill, Dr. Luca Buzzetti (freshly arrived from the Melchiorre group), and Mikus Purņš, a new Ph.D. student and fresh master from Maris Turks's group (another former Trost postdoctoral researcher) (section 6). After two years of effort, this last project was successful.¹³ Interestingly, the lead result was obtained with a DACH-type Trost ligand, a class of ligands developed for triple A reactions,² which had also been used by our group.¹⁴ However, the best ligand was surprisingly a 'one-arm' phosphine truncated derivative **1**, which had previously been useless in catalysis.

To give a different insight into the story of palladium in our laboratory, I decided to give a green card for writing to the group members who were involved in the daily research, and to designate them as corresponding authors for the related section. This should give valuable and different insights into the daily fight and the up-and-down phases in an organic-chemistry laboratory.

2 Oxy- and Aminoalkynylation of Olefins (Dr. Stefano Nicolai)

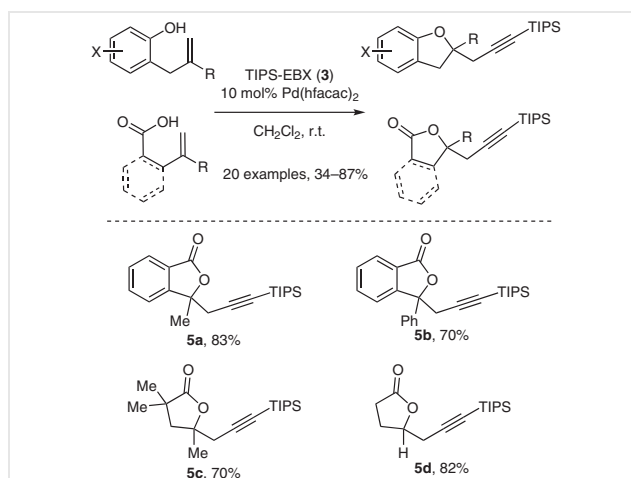
When I joined Professor Waser's group in 2009, it was with much enthusiasm that I accepted the opportunity to start my doctoral research work by investigating the application of palladium catalysis to the intramolecular oxyalkynylation of olefins. As mentioned in the Introduction, Stéphane Erard had already obtained encouraging preliminary results. As a proof of concept, he had found that the isopropenyl phenol **2a** could be cyclized to give propargylic dihydrobenzofuran **4a** in 6% yield by using a palladium salt as the catalyst with an alkynyl iodonium compound as an electrophilic alkynylating species (Scheme 3). When I took over the project, he had completed a first round of screening, revealing the superiority of the electron-deficient complex bis(hexafluoroacetylacetonato)palladium [Pd(hfacac)₂] in combination with the neutral hypervalent iodine reagent TIPS-EBX (**3**). Starting from the highly promising 25% yield that he obtained when the reaction was performed in methanol, a rapid screening of conditions allowed me to confirm that Pd(hfacac)₂ was the best catalyst and to identify dichloromethane as the optimal solvent.⁷ Substrate **2a** had been initially selected based on the hypothesis that competing β-hydride elimination might have resulted in suppression of the desired alkynylation step. We were therefore pleased to find that phenol **2b**, which is prone to such a side reaction, was also a competent substrate for the oxyalkynylation, albeit leading to a lower 46% yield of **4b**.



Scheme 3 Discovery and optimization of the oxyalkynylation of isopropenyl phenols **2** with TIPS-EBX (**3**) under Pd(II) catalysis

The same set of optimized conditions could be then applied to diversely substituted isopropenyl phenols and was subsequently extended to alkenylbenzoic acids, which were satisfyingly converted into propargyl phthalides (e.g., **5a** and **5b** in Scheme 4).

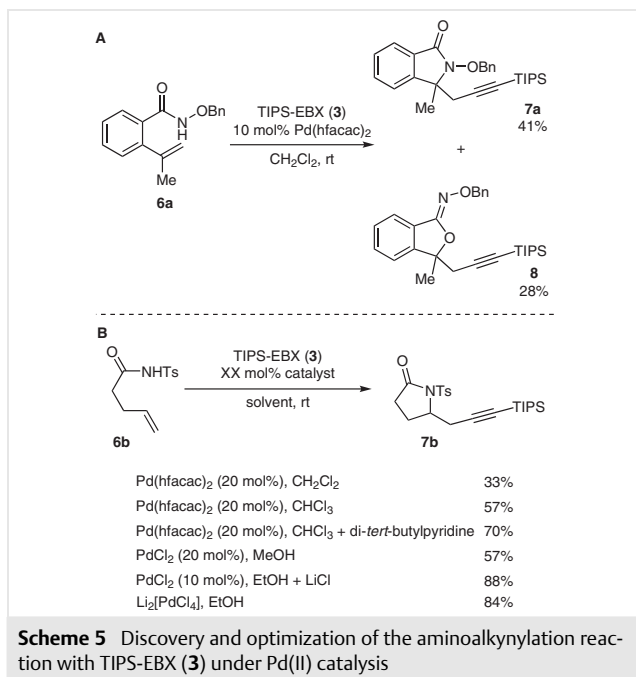
With a broad scope to sustain the value of our new transformation, we were reasonably confident that we had secured a high-impact publication. The contrary opinion of the reviewers prompted us to consider olefin substrates that appeared highly unlikely to react under our conditions: aliphatic alcohols and carboxylic acids. Whereas the former remained resistant to the transformation, at least under



Scheme 4 Selected scope of the oxyalkynylation reaction

Pd(II) catalysis (but see below), various pentenoic acids were found to undergo the oxyalkynylation with 70% yields (for example, **5c** and **5d** in Scheme 4). Such highly flexible compounds reacted much faster than the previously surveyed ones, demonstrating that: (a) a more acidic character of the aliphatic CO₂H group makes it more reactive; (b) the entropic gain provided by the rigid structure of aromatic olefins is not a strict requirement for the success of the cyclization. In addition to this, a most valuable result was obtained with unsubstituted pent-4-enoic acid, whose oxyalkynylation occurred in high yield to give **5d**, despite a competitive β-hydride elimination. This observation had also an important impact when setting the basis of the subsequent project.

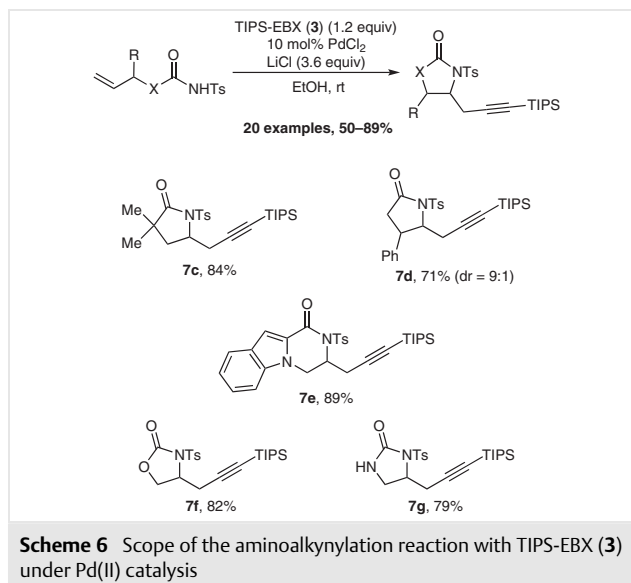
Having established a solid protocol for the oxyalkynylation of alkenyl phenols and carboxylic acids, the development of a 'nitrogen variant' of this reaction appeared a likely obvious spinoff and an exciting challenge at the beginning of the second year of my Ph.D. While I was still investigating the scope of the oxyalkynylation, evidence of the viability of a potential aminoalkynylation reaction had been provided under the same conditions by the successful cyclization of the benzyl hydroxamate **6a**, although poor N versus O chemoselectivity was observed with this compound (see products **7a** and **8** in Scheme 5A).⁷ With pent-4-enoic acid now known to be an effective (and readily available) substrate, I decided to direct my attention to various N-activated pentenamides in a search for a model to study the aminoalkynylation. This was the right move: after few unsuccessful attempts, easily accessible *N*-tosylpent-4-enamide (**6b**) emerged as the ideal candidate for an investigation of the new reaction. In fact, when I submitted it to reaction with TIPS-EBX (**3**) in the presence of catalytic Pd(hfacac)₂, the desired propargylic lactam **7b** was isolated in an encouraging 33% yield (Scheme 5B).⁸



However, the hope of another rapid optimization soon faded. A first significant yield improvement, up to 57% yield, was made possible by switching the solvent from dichloromethane to chloroform while still using Pd(hfacac)₂ as the catalyst. Another improvement came from a survey of several additives, among which 2,6-di-*tert*-butylpyridine led to a 70% yield.

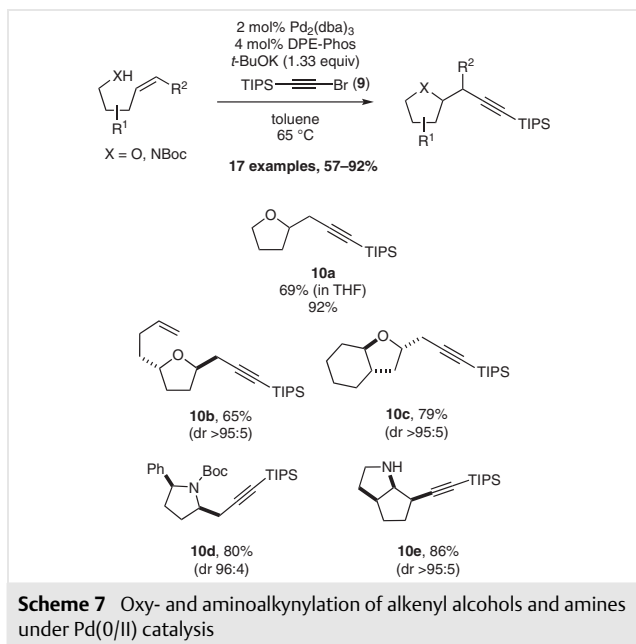
However, it soon became clear that changing the catalytic species had to be considered to achieve optimal conditions. In the end, we were pleased to discover that the simplest and least-expensive palladium source, PdCl₂, was the catalyst of choice; an optimal set of (operator-friendly) reaction conditions were then found; these included ethanol as the solvent and an excess of LiCl as an additive, providing the expected propargyl lactam in excellent 88% yield. A similar result, obtained upon using commercially available Li₂[PdCl₄], strongly supported the hypothesis that the latter might be the actual active catalytic species, formed *in situ* under the reaction conditions.

The newly established aminoalkynylation protocol was shown to work efficiently with a broad scope of substrates (Scheme 6), giving access to γ - and δ -lactams (**7c–e**) in good to excellent yields. The reaction could also be extended to carbamates and ureas (**7f** and **7g**), which can be seen as early examples of the tethering strategy later developed within our group. The propargyl-containing heterocycles generated through this method could be then used in an expedient synthetic sequence to access pyrrolizidine and indolizidine scaffolds, demonstrating the preparative utility of the aminoalkynylation reaction.



With both oxy- and aminoalkynylation methods now working well with, respectively, olefin-containing carboxylic acids and *N*-tosyl amides, for the rest of my Ph.D. studies, I decided to return to the problem of less-oxidized O- and N-nucleophiles. Alkenyl alcohols and amines had been found to react sluggishly under conditions relying on high-oxidation-state Pd catalytic manifolds and TIPS-EBX (**3**) as the alkynylating species. The best result I could collect was, in fact, a less than 20% yield obtained in the oxyalkynylation of pent-4-enol with Pd(hfacac)₂. It was at this moment that my interest was caught by the reports from Wolfe and co-workers on Pd(0/II) oxy- and aminoarylation reactions.¹⁵ On the basis of those works, I reasoned that the use of a more electron-rich palladium catalyst might be more compatible with less-oxidized nucleophiles. At the same time, less electrophilic alkynylating reagents, such as acetylene halides, might be more suitable. This fact was considered to be an advantage from the synthetic point of view, considering the rather complex protocols then available for the preparation of EBX reagents (and their still-limited variety). This intuition proved correct: when I first submitted pent-4-enol to reaction with TIPS-ethynyl bromide (**9**) in the presence of a catalytic amount of tris(dibenzylideneacetone)dipalladium(0) [Pd₂(dba)₃] with bis[(2-diphenylphosphino)phenyl] ether (DPE-Phos) as ligand, I was able to isolate the desired propargylic tetrahydrofuran **10a** (Scheme 7) in very good 69% yield by using THF as the solvent.^{9a} This very promising result definitively convinced us that it was time to drop Pd(II)/TIPS-EBX (**3**) and to adopt Pd(0/II)/Br-acetylenes as a potentially more rewarding alkynylating system. Optimizing the oxyalkynylation of pent-4-enol required only a minimal effort. Although various solvents, palladium sources, and solvents were tested, it sufficed to simply switch from THF to toluene to perform the reaction

in an excellent 92% yield. Under these optimal conditions, the reaction worked efficiently with a broad variety of alkenols. Notably, by starting from secondary alcohols, the corresponding *trans*-2,5-disubstituted tetrahydrofurans **10b** and **10c** were formed. The protocol could also be directly extended to the cyclization of *N*-protected amines, which were efficiently converted into the corresponding pyrrolidines **10d** and **10e**. This is of particular interest, especially when considering that, in palladium catalysis, moving from oxygen to nitrogen nucleophiles generally requires a laborious retuning of most parameters.



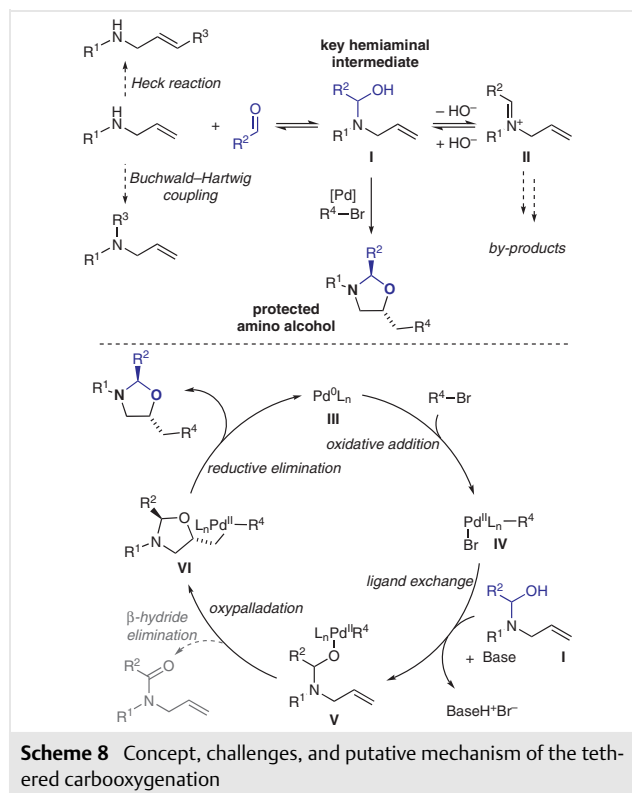
The remainder of my doctoral investigations essentially focused on a further expansion of the scope of the Pd(0/II)-catalyzed nucleoalkynylation of alkenes to include aliphatic bromoacetylenes as an alternative to brominated silyl alkynes.^{9b} The preliminary results that I collected on the carboalkynylation of alkenyl-containing malonates represented, instead, a starting point for the master's work of Peter Swallow, when he joined the group in 2012.^{9c}

3 In Situ Tethering Strategies for the Synthesis of Vicinal Amino Alcohols and Diamines (Dr. Ugo Orcel)

When I started my Ph.D. studies in 2012, Stefano was already away from the bench and close to finishing the writing of his thesis. His work had paved the way for future developments of Pd-catalyzed olefin difunctionalizations in the Waser group. My initial goal was to extend the scope of oxy- and aminoalkynylation to a fully intermolecular process. After a broad screening of olefin substrates and nucle-

ophiles, a hit was found that involved styrene, alcohols, and TIPS-EBX (**3**). Unfortunately, this system had strong limitations. One of these was the need for a large excess of olefin and alcohol to obtain a good conversion to the desired oxyalkynylation product.¹⁶ It was apparent that this system was lacking in both reactivity and selectivity, which are typical challenges in multicomponent reactions.

During my investigations, I became aware of the work of the Beauchemin group on Cope-type hydroamination of allylamines.¹⁷ Aldehydes are employed to form a mixed aminal in situ, which then undergoes a facilitated retro-Cope elimination. The singularity of their strategy is the in situ installation and cleavage of the tether, which avoids the tedious extra steps usually required to install and remove the tether. That was very intriguing and it opened new perspectives for my work. Indeed, applying such strategy by combining an allylamine and an aldehyde tether would form an hemiaminal in situ, the oxygen of which would serve as a source of oxygen for the oxypalladation (Scheme 8). This might permit a significant rate acceleration and a higher selectivity for the olefin difunctionalization process by reducing the entropic penalty and by preorganizing the substrate.



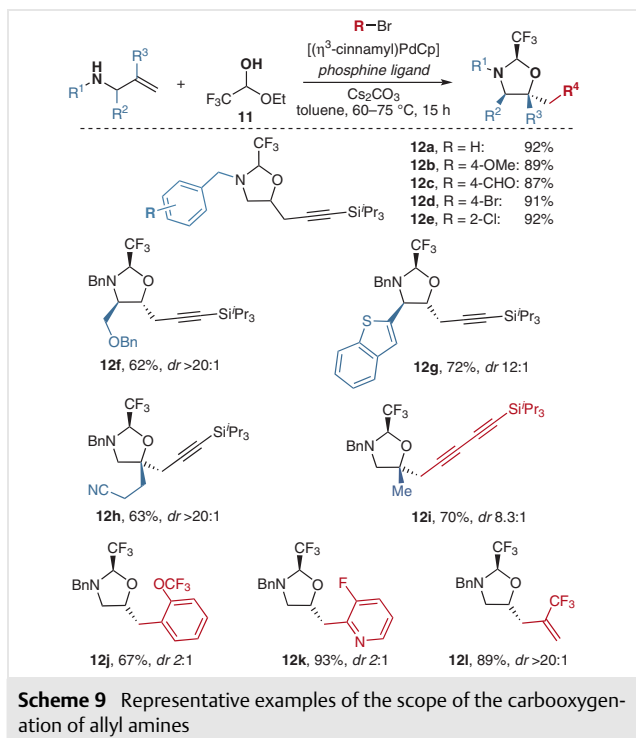
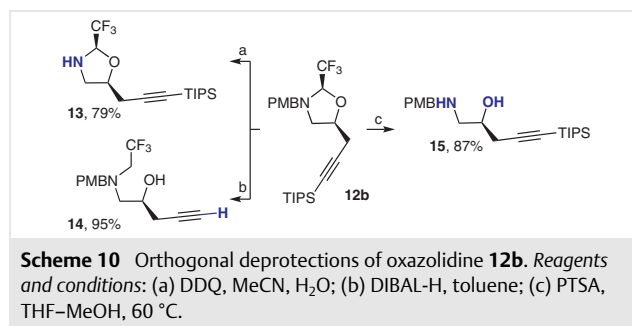
The working hypothesis and possible side reactions are shown in Scheme 8. First, a key to the success of the envisioned reaction is the fast formation of a stable hemiaminal **I**. Indeed, the allyl amine could undergo undesired Heck or

Buchwald–Hartwig cross-coupling reactions in the presence of a Pd catalyst, or could deactivate it. Thus, hemiaminal **I** should be both kinetically and thermodynamically favored over the allyl amine and the iminium **II**. Acyclic hemiaminals can be stabilized by electron-withdrawing groups on the nitrogen, as well as on the ketone or aldehyde partner.¹⁸ However, the reduced nucleophilicity of the allyl amine could also hamper the formation of the hemiaminal. Secondly, the hemiaminal must also engage in the Pd-catalyzed carboxygenation process to yield oxazolidines as protected amino alcohols. The putative mechanism starts with the oxidative addition of an organohalide by a Pd(0) complex **III** to form the complex **IV**. Ligand exchange generates the Pd(II)-alkoxide **V**. Then, the key oxypalladation occurs to form **VI**. Alternatively, an undesired β -hydride elimination could yield an amide. A final reductive elimination step permits the formation of the desired oxazolidine and regenerates the Pd(0) catalyst.

To test this approach, I selected (a) two allyl amines with either an electron-withdrawing group (Cbz) or an electron-rich group (Bn), and (b) three aldehydes with different stereoelectronic properties: formaldehyde, benzaldehyde, and 2,2,2-trifluoroacetaldehyde (fluoral) in its stable ethyl hemiacetal form **11** (Scheme 9). I was pleased to find that employing Stefano's Pd⁰/Pd^{II} conditions allowed me to identify a hit with the combination of the *N*-benzylallylamine and fluoral ethyl hemiacetal (**11**), which delivered a 32% yield of the desired oxazolidine **12a**. Other aldehydes or ketones tested were not superior. The choice of carbonate base, Pd precatalyst, and phosphine ligand proved also to be

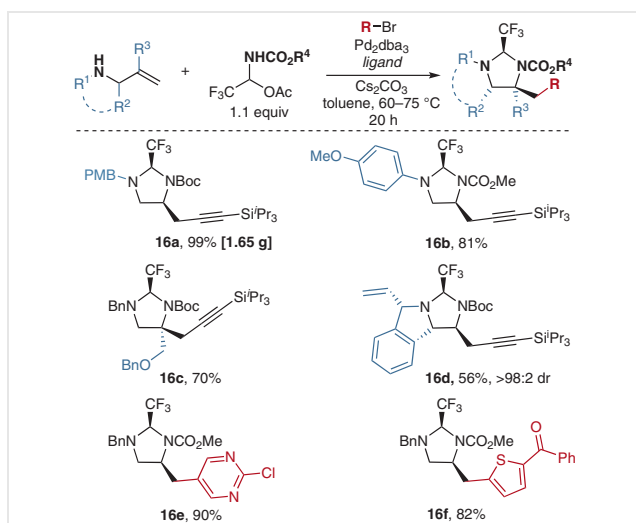
critical.^{10a} Each class of allyl amine substrates [simple allyl amines (**12a–e**), α -branched allyl amines (**12f** and **12g**), and geminally disubstituted olefins (**12h** and **12i**)] required a dedicated ligand. The scope of the reaction was broad with respect to both the allyl amine and bromide: α -branched allyl amines and geminally disubstituted olefins gave the corresponding oxazolidines **12f–i** in good yields. Electron-deficient aryl and vinyl bromides were also suitable partners in the carboxygenation process (**12j–l**). Interestingly, the transformation was often highly diastereoselective, which was a hint that the hemiaminal stereocenter could be epimerized, probably through iminium formation, before the oxypalladation occurred. Hence, a DYKAT might be possible with the use of a suitable chiral Pd catalyst.

The synthetic potential of this methodology was demonstrated by selective conversion of product **12b** into (a) the free amine **13** by oxidative cleavage of the PMB protection, (b) the free alcohol **14** by reductive opening of the hemiaminal, or (c) the free amino alcohol **15** by hydrolysis (Scheme 10).



The logical continuation was the development of a tethered carboxamination to access diamines, which are extremely valuable building blocks. To this end, an aldimine would be used instead of an aldehyde to form a mixed aminal intermediate, which would then undergo a carboxamination to deliver versatile imidazolidines. I initially focused my efforts on identifying a suitable secondary aldimine tether. Although the range of aldimines that could deliver the desired imidazolidines was wider than that in my previous project with aldehydes, only the combination of a CF₃ moiety and a carbamate protecting group provided full conversion and high yields (Scheme 11).^{10b} In contrast to the previous hemiaminal intermediates, the mixed aminals were stable enough to be isolated.

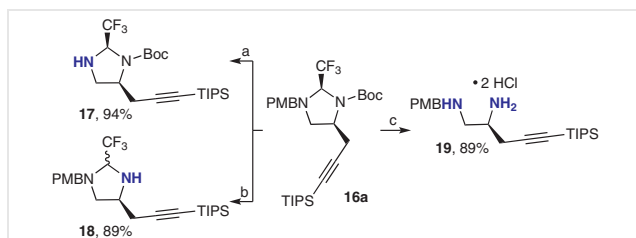
The catalytic system involved Pd₂dba₃ and mainly tris(2-furyl)phosphine [P(2-furyl)₃] as a ligand. Unlike the synthesis of amino alcohols, this method tolerated both primary and secondary aliphatic allylamines substrates, and also a less-nucleophilic aniline derivative **16b**. The α -tertiary amine **16c** could also be accessed, provided 2'-(diphenylphosphino)-*N,N'*-dimethyl-(1,1'-biphenyl)-2-amine (PhDavePhos) was used as a ligand. CsOTf as an additive was crucial to obtain a high conversion for more hindered



Scheme 11 Representative examples of the scope of the carboamination of allylamines

α -substituted allylamines, such as the complex imidazolidine **16d**. CsOTf was also efficient in limiting or suppressing the undesired Heck reaction when aryl bromides were employed. Thus, a large variety of aryl and hetaryl groups could be introduced in high yields, including pyrimidine (**16e**) and thiophene groups (**16f**).

The free amines **17** and **18** could be accessed selectively from imidazolidine **16a** by a suitable choice of the reaction conditions (Scheme 12). Alternatively, full tether removal was achieved by heating in a microwave oven at 160 °C followed by addition of HCl in methanol to give **19**.



Scheme 12 Orthogonal deprotections of imidazolidines **16a**. Reagents and conditions: (a) DDQ, MeCN, H₂O; (b) microwave irradiation (160 °C), EtOH–H₂O; (c) HCl, MeOH.

The success of these two methodologies stems largely from the unique effectiveness of CF₃-based tethers. Their high electrophilicity and compact size permit (a) fast and quantitative (hemi)aminal formation in combination with nucleophilic allylamines, and (b) the required stabilization of the resulting (hemi)aminal, while retaining sufficient nucleophilicity to undergo the carboxylation and carboamination processes. Furthermore, the increased acidity of the nucleophiles allows mild carbonate bases to be used

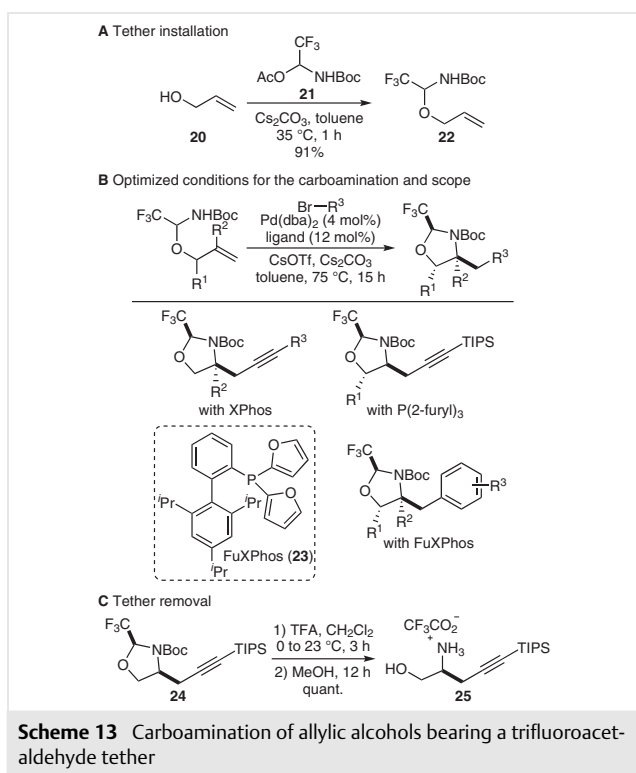
and, consequently, the reactions tolerate many functional groups.

4 Carboamination of Allylic Alcohols (Bastian Muriel)

I joined the LCSO group in January 2016 for my master's thesis, to investigate new palladium-catalyzed olefin functionalizations under the supervision of Ugo. After several unfruitful investigations towards the carboamination of fluoroolefins, we turned our attentions toward allylic alcohols, hoping that we could extend the tethering strategy successfully developed by Ugo with allylic amines. Our interest in developing such a transformation was that it might lead to 1,2-amino alcohols that were structurally complementary to those obtained in Ugo's first project.

The first challenge of this work was to find a suitable tether to be introduced on the alcohol, due to its lower nucleophilicity compared with amines. Drawing inspiration from the literature,¹⁹ we installed various tethers on allyl alcohol **20**, and we found that Ugo's tether **21** derived from trifluoroacetaldehyde permitted the formation of the corresponding hemiaminal ether **22** in the highest yield (Scheme 13A).¹¹ Moreover, under conditions easily reoptimized from Ugo's last work, the presence of a trifluoromethyl substituent on the tether and of a Boc-protecting group on the nitrogen were key to attaining high yields in the carboamination reaction. Although I was able to achieve a one-pot tether installation/carboamination with allyl alcohol **20**, the overall yields that I obtained remained lower than with allylamines, despite my efforts to optimize this transformation. Consequently, after discussions with Professor Waser, we decided to investigate this novel carboamination from preformed hemiaminal ethers. The second challenge of this project was to find an appropriate phosphine-based ligand to ensure the highest yields and chemoselectivity, depending on the substitution on the allylic alcohol as well as the nature of the electrophilic partner (Scheme 13B). Luckily, in combination with bromoalkynes, substituted allylic alcohols delivered the corresponding oxazolidines in high yields and diastereoselectivities in the presence of a commercial ligand: dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl) phosphine (XPhos) or P(2-furyl)₃. When aryl bromides were used, however, all the commercial phosphine-based ligands that I surveyed led to the formation of a Heck by-product along with the desired aminoarylation. Although not optimal in all parts of the scope that Ugo explored for his carboamination of allylic amines, the use of P(2-furyl)₃ often permitted the formation of the desired products in decent yields. Ugo therefore had this idea of introducing furyl substituents onto phosphine-based Buchwald-type ligands, in the hope that this would be beneficial. He then synthesized a library of furyl-substituted monophosphine ligands that I could test in the aminoarylation that I aimed

to develop. Gratifyingly, I found that FuXPhos (**23**) suppressed the competing Heck reaction and permitted selective formation of the aminoarylation products in good yields. Moreover, I could obtain even higher yields by the addition of cesium triflate as an additive, an idea previously reported by Wolfe and co-workers,¹⁵ and also implemented by Ugo.^{10b} Under these conditions a wide range of electron-deficient aryl bromides were successfully engaged in the transformation. Eventually, we could easily remove the trifluoroacetaldehyde-derived tether from product **24**, to access the corresponding amino alcohol **25** in quantitative yield (Scheme 13C).

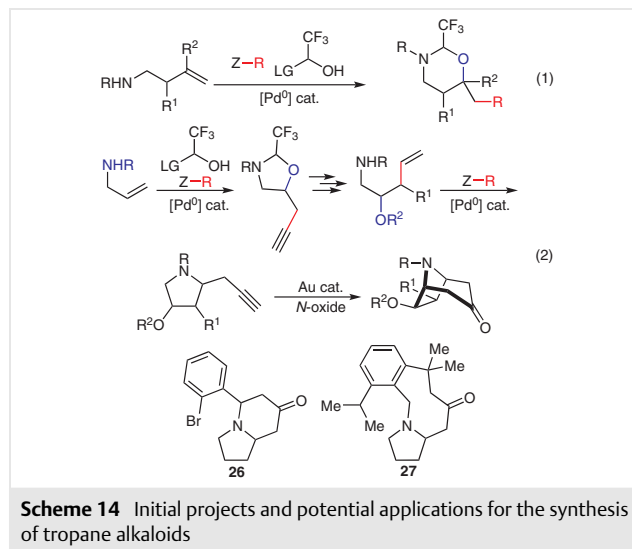


Scheme 13 Carboamylation of allylic alcohols bearing a trifluoroacetaldehyde tether

5 Carboxygenation of Propargylic Amines (Dr. Phillip D. G. Greenwood)

I joined the Waser group in October 2015, after spending the previous four years at Imperial College London, and I was immediately taken with the size and space at EPFL. At our meeting after joining the group, Jerome laid out the options for possible projects for me. One of these options seemed like a logical development of work recently published by the group. This was to develop Ugo's tethered carboxygenation on the homologated alkene amine system, with the aim of accessing 1,3-amino alcohols (Scheme 14, eq. 1). As Ugo had already demonstrated the feasibility of the transformation (with low but promising yields of what was thought to be the desired product), this felt like a good project with which to start my Ph.D. studies. After several

months of fruitless effort (never exceeding the 13% NMR yield obtained by Ugo), we decided to shelve that particular project.

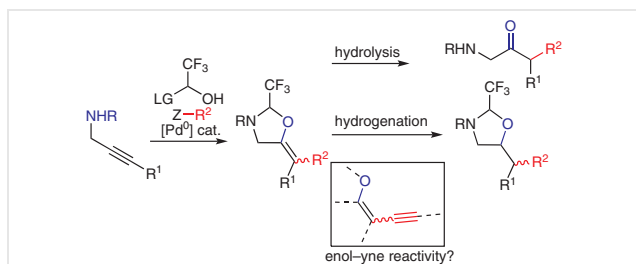


Scheme 14 Initial projects and potential applications for the synthesis of tropane alkaloids

For my second project, I wanted to have a go at total synthesis, and I devised a route to a family of tropane alkaloids (Scheme 14, eq. 2) utilizing the work of Stefano and Ugo. While there were quite a few steps (>12) to achieve a small and low-complexity product, I hoped that my route would offer sufficient flexibility and that some of the steps could be removed while showcasing the work done in the group. Unfortunately, while testing a model substrate on the final key reaction involving gold carbene formation from the alkyne, as developed by Liming Zhang,²⁰ the intramolecular cyclization occurred preferentially on the benzylic protecting group rather than the pyrrolidine ring to give **26** and **27**. Although other strategies might have been able to provide the desired tropane scaffold, at this point I had lost interest in the project and in the synthetic strategy that I had devised.

At this stage, Ugo had published his paper on carboamylation with allylic amines,^{10b} and I went back to considering possible ways to develop the chemistry. Replacing the allylic amine with a propargylic amine looked like it might be an interesting modification (Scheme 15). If the reaction was to proceed, then the product formed would contain an additional site of unsaturation in the form of an enol-yne, and if the products were stable, they might provide a platform for an array of further product modifications, for example through hydrolysis or hydrogenation.

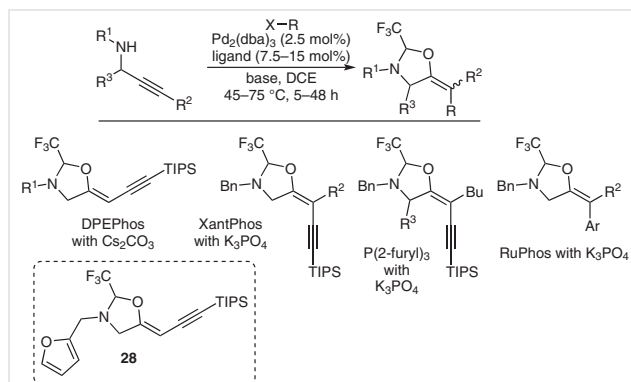
One of the selling points of the tether strategy is that the trifluoroacetaldehyde-derived tether is cheap and commercially available. The bromo(triisopropylsilyl)alkyne is easily obtained in one easy step, and its purification essentially involves a filtration through silica gel. The propargylic amines on the other hand were a pain to make during the



Scheme 15 Carboxylation of propargyl amines and potential applications

next three years, as only two of the working starting materials was commercially available (neither of which were model substrates). Several different strategies were used with varying success, with the routes via tertiary amines leading to the easiest purification. Finally, by knowing which of the many reported synthesis protocols really works well for each class of substrates, the starting materials can be made efficiently in a few steps.

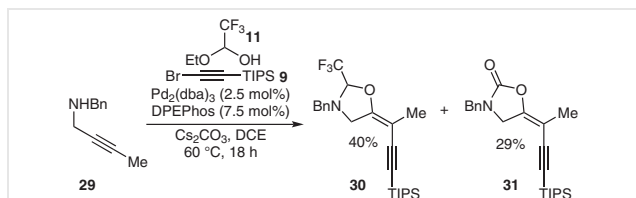
I started with the terminal propargylic amine, as it provided the closest fit to the successful allylic amines, and I tested the conditions from Ugo's publication.^{10a} This immediately supplied us with promising results that, after optimization of the solvent and ligands, were improved to give good yields (Scheme 16).^{12a} A screening of conditions quickly showed that a change of solvent to DCE gave an improvement in yield and product selectivity, but changes in the other conditions did not lead to any further improvements. The trisubstituted alkene product could be isolated by chromatography but removing all impurities was initially a challenge. It became obvious that the compound was acid sensitive, as it discolored in untreated chloroform and it left a stain on the silica gel if the column was paused for too long; however, the product was too apolar to have any triethylamine present. I ended up with a process involving treating silica gel with a triethylamine solution, drying the column, and running a 0–1% ethyl acetate-in-pentane gradient. From the product NMR, we saw that two product isomers were formed. These could be partially separated by preparative TLC, but we initially had no idea which isomer was which. I started on a study of the scope of various protecting groups, hoping that one of them might give a crystal, but all the products were oils. However, only a month or so after starting the scope study, on looking back through the vials, I noticed that a product with an *N*-methylfuryl group (**28**) had solidified, with some partially formed crystals on the wall of the vial. I was unable to recrystallize this product due to its high solubility, but the flecks of crystals adhering to the vial were enough to enable the X-ray crystallography team to perform an analysis and to tell us that the major isomer was the *Z*-isomer, indicative of a *syn*-oxy-palladation.



Scheme 16 Carboxylation of propargylic amines

At about the same time that I was developing conditions for the terminal propargylic substrate, I explored the reaction with the internal propargylic amine **29** (Scheme 17). Success with this substrate would allow access to products with substitution patterns not achievable through the use of allylic amines. Again, the conditions from the allylic amine project immediately gave promising results, and again, changing the solvent to DCE led to a dramatic improvement in the yield of product **30**, but also highlighted the formation of the byproduct **31**. NMR studies indicated that the byproduct had a greater planarity than the target product, and alkene and alkyne peaks were visible in the ¹³C NMR spectrum. The MS showed a mass of the starting material with the addition of TIPS-alkyne and CO₂, and the IR spectrum showed the presence of a C=O bond, allowing us to assign the structure **31** to the byproduct. But where was CO₂ coming from? All the reactions were being carried out under N₂, and the systems were degassed quite stringently before carrying out the reaction. But I was using a carbonate base! As unlikely as it seemed, cesium carbonate was acting as a source of the CO₂ unit to form a cyclic carbonate. This was unexpected and interesting, but unwanted. The obvious change to make was to use an alternative base in the reaction, one that would not form CO₂ in some way. A variety of bases were tested, and potassium phosphate gave the first good hit. I played around a bit at trying to use cesium phosphate prepared either by simple acid–base reaction or with the use of a furnace. Although the furnace-produced cesium phosphate gave promising results, analysis determined it to be a mix of the di- and tribasic salt (whereas the acid–base reaction led primarily to dibasic potassium phosphate). The use of the furnace, while entertaining, was felt to be a bit impractical for implementation in a methodology that I hoped others would later apply. An initial test with potassium phosphate did give trace amounts of the carbamate, but the bottle that I used looked rather old, a new bottle was purchased and, as hoped, gave a better yield with no carbamate formation. Carrying out

some additional optimization led to an additional change of the ligand to 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (XantPhos) (see Scheme 16).

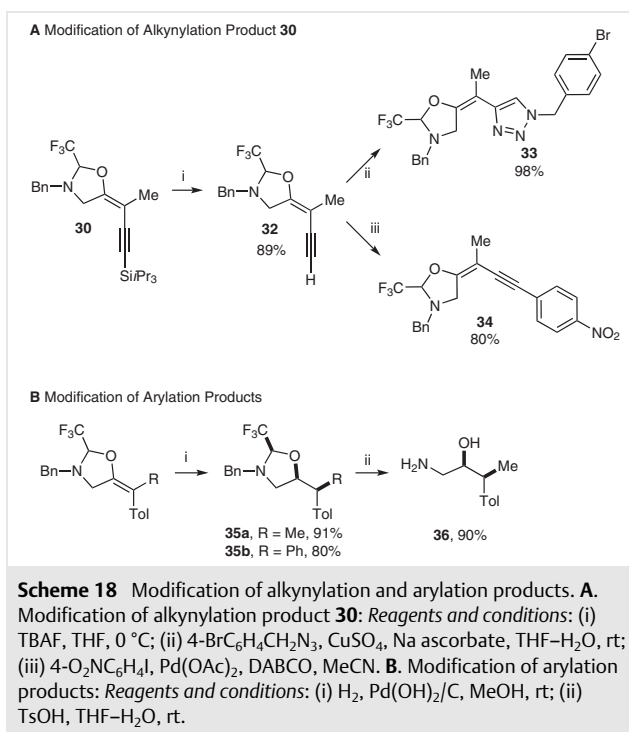


Scheme 17 Carboxygenation of propargylic amine **29**. Unexpected formation of CO₂-incorporated byproduct **31**.

While studying the scope of the reaction, we saw that the *E/Z* ratio was highly dependent on the substituents of the alkyne, with bulky *tert*-butyl or aromatic groups giving one product exclusively. The NMR data indicated that the major isomer was the opposite of the terminal propargylic amines, but we did not have a clear evidence for this, as the products were still being obtained as oils. At this point, I considered that it could be useful to do some derivatizations on product **30**, as this might be able to provide crystals for analysis (Scheme 18A). The free alkyne **32**, obtained after the removal of the triisopropylsilyl group, still gave an oil. To my surprise and frustration, the product **33** of the copper-catalyzed click reaction between the free alkyne and 4-bromobenzyl azide still gave the product as an oil. Luckily, I was able to get a reasonable crystal structure from the Sonogashira coupling product **34**. The results of the analysis showed that, indeed, the *E/Z* selectivity had switched indicating a potential change in the mechanism.

The addition of substitution at the propargylic position required another screening of conditions for the alkyne, revealing that, in this case, monodentate tri(2-furyl)phosphine was optimal for the reaction (Scheme 16).

I had the good fortune to collaborate a short time with Dr. Erwann Grenet, who carried out a large part of the work involving aryl electrophiles and internal propargylic amines. I had made some efforts toward the reaction of terminal propargylic amines with aryl electrophiles, with limited success. The most useful information obtained was that here, Buchwald-type ligands performed better than standard mono- or bidentate phosphine ligands (Scheme 16). Otherwise the reactions led to low yields and mixtures of products. Dr. Grenet was able to develop conditions using aryl iodides and internal propargylic amines; the use of 2-(dicyclohexylphosphino)-2',6'-diisopropoxybiphenyl (RuPhos), potassium phosphate, and a lower temperature, led to good yields of single products. A variety of aryl iodides reacted successfully, with both electron-donating and electron-withdrawing groups being tolerated (unlike previous chemistry), as well as various groups on the propargylic alkyne. The main byproduct from these reactions was that of protodemetalation of the vinyl-palladium species. One of

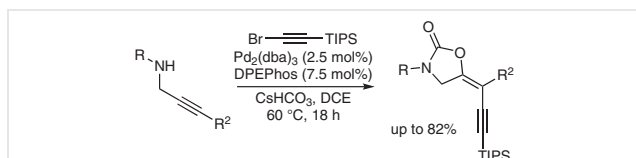


Scheme 18 Modification of alkyne and arylation products. **A.** Modification of alkyne product **30**: *Reagents and conditions*: (i) TBAF, THF, 0 °C; (ii) 4-BrC₆H₄CH₂N₃, CuSO₄, Na ascorbate, THF–H₂O, rt; (iii) 4-O₂NC₆H₄I, Pd(OAc)₂, DABCO, MeCN. **B.** Modification of arylation products: *Reagents and conditions*: (i) H₂, Pd(OH)₂/C, MeOH, rt; (ii) TsOH, THF–H₂O, rt.

the products gave a crystal, allowing us to determine that the isomer formed in the reaction is exclusively that from a *trans* oxy-palladation. Dr. Grenet proceeded to carry out the hydrogenation of the resulting arylation products as entries for the product modification (Scheme 18B). The hydrogenation led to an unexpected outcome. We saw that the chosen heterogeneous Pd catalyst gave single diastereomers of the products **35a** and **35b**, detectable by NMR; these could both be easily deprotected to give amino alcohol **36**. It was this observation that inspired me to pursue an enantioselective transformation at the end of my Ph.D. studies (section 6).

Earlier, in the optimization of the oxyalkynylation with internal propargylic amines, I saw that the cyclic carbamate **31** was formed as a byproduct in the absence of gaseous CO₂ (Scheme 17). This was both surprising and interesting, as I had not seen a metal carbonate act in such a way with palladium catalysis, and I thought it might be an interesting reaction to explore further. Other than the work published by Nevado and co-workers,²¹ there were no other palladium-catalyzed cyclic-carbamate-forming reactions from propargylic amines that proceeded through a dual functionalization of the alkyne. The key role of the base as the source of CO₂ in the reaction was the starting point for screening. Some screening reactions of bases and temperature (performed with some help from three first-year master's students at EPFL) showed that the use of CsHCO₃ at 60 °C delivered up to 82% isolated yield of the cyclic carbamates (Scheme 19).^{12b} Two interesting observations emerged from the optimization. First, the reaction could be run with a single equivalent of cesium hydrogen carbonate with only a

small drop in conversion, and secondly, the reaction showed no improvement when additional CO₂ was introduced into reaction from a balloon. In our publication, we hypothesized a novel mechanism that does not involve molecular CO₂.^{12b} The scope study was carried out with a variety of different substituents on the nitrogen or alkyne of the propargylic amine, but attempts to use other electrophile coupling partners were, unfortunately, unsuccessful.

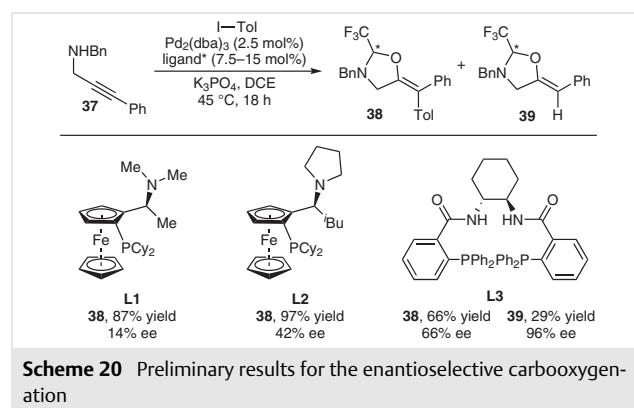


Scheme 19 Carboxylation of propargyl amides with CsHCO₃ as tether precursor

6 Enantioselective Carboetherification/Hydrogenation through a Catalytically Formed Chiral Auxiliary (Dr. Phillip D. G. Greenwood, Dr. Luca Buzzetti, Mikus Puriņš)

Phill: The seemingly perfect diastereoselectivity of the hydrogenation carried out on the arylation product had been sitting at the back of my mind since we first observed it, and I had finished the carboxylation project with six months of my Ph.D. studies to go. After seeing that the amino alcohols resulting from the hydrogenation of these products would be pharmaceutically active, and that these products would be difficult to obtain enantiomerically by other means, I realized that if I was able to install the CF₃-containing tether enantioselectivity, this would open up a route to a series of alkyl-aryl and diaryl amino alcohols. In addition, I had noticed from ¹H NMR spectroscopy that, with the propargylic amines, the tether adds reversibly to the amine, potentially permitting a dynamic process to take place. After screening a series of chiral mono and bidentate phosphine ligands, ferrocene-based Josiphos-type ligands with alkyl phosphines demonstrated potential in the carboxylation reaction of amine **37**. During the next several months, with the invaluable aid of Luca, I attempted to access a range of ligands based on the Josiphos scaffold (see below for details of Luca's part of these studies). Not only were we contending with the problem of obtaining good yields and enantioselectivities of the desired product **38**, but also with that of the formation of the protodemetalation byproduct **39**, inseparable by chromatography (Scheme 20). It was only at the suggestion of Jerome, who pointed out that it can sometimes be a good idea to test the intermediates of the target ligand, as they can also show activity, that we submitted the P,N-ligand **L1** to the reaction and, to my amazement and delight, this completely shut down the formation of the protodemetalation byproduct and gave the desired product in good yield with a small

amount of enantioenrichment. Months of work were put into variations of the phosphine, amine, and side group, but the peak was achieved with ligand **L2**. Some other potential ligand types were tried with limited success. Again, Luca saved the day by convincing me to try a ligand class that I had missed out on my initial screening: the Trost ligand **L3**. Immediately, the enantioselectivity surpassed any previously obtained, and was accompanied by a good yield; the only problem was that the protodemetalation byproduct was once more being formed. I tried other commercial Trost ligands with alternative backbones and side arms, but at this point I had run out of time in the laboratory and had to start moving toward writing my Ph.D. thesis. After handing over my hood and introducing Mikus to the chemistry, I had to take a back seat, as he and Luca took it forward.

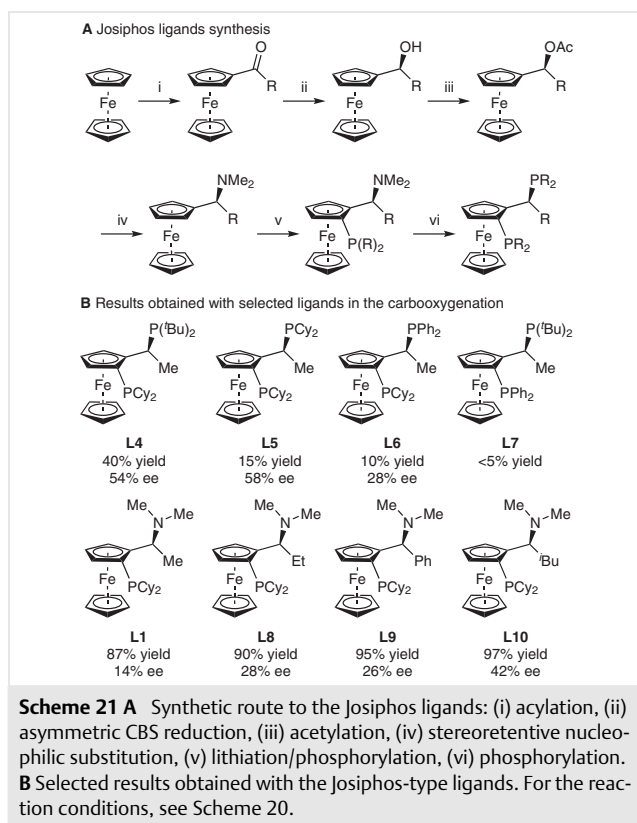


Scheme 20 Preliminary results for the enantioselective carboxylation

Luca: I joined the LCSO group in January 2019 as a post-doctoral researcher incorporated in the 'tethering funding scheme'. This meant I could work on the development of palladium-catalyzed reactions, a field of research that I had never explored before. Since my very first days in the laboratory, I had found particularly intriguing the results obtained by Phill, showing a transfer of the stereochemical information during the catalytic hydrogenation of the enantioenriched product **38**. Remarkably, the CF₃ group, introduced with the tether in an enantioselective fashion, perfectly controlled the stereoselectivity of the subsequent reduction: in short, we were exploiting asymmetric catalysis in the carboetherification step to build up a transient chiral auxiliary. At that point, the goal was clear: optimize this step both in terms of yield and enantioselectivity to make the whole process efficient and useful – 'a few weeks' task'. Unfortunately, my previous experience in the field of (photo)organocatalysis was putting me in a slightly less optimistic mood.

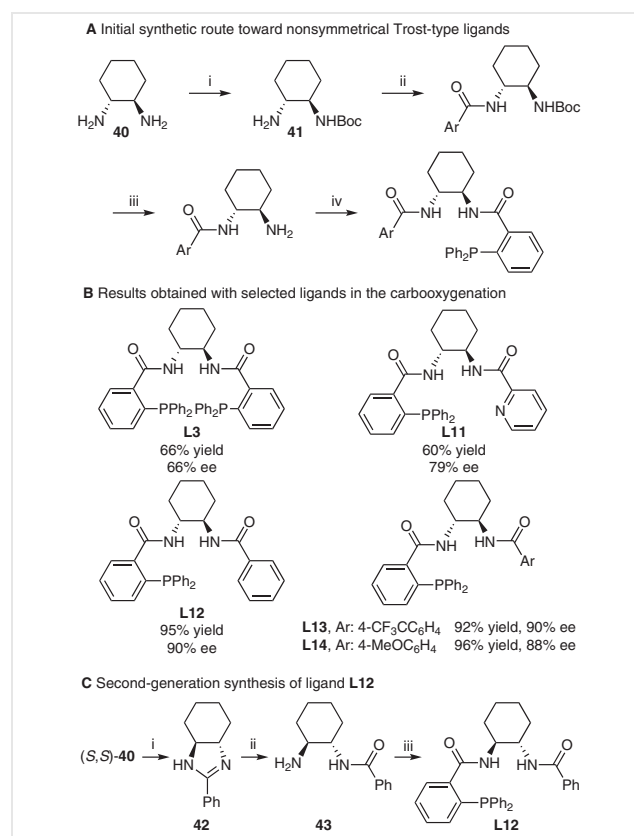
First, we started a search for the best ligand for this DYKAT. Our preliminary results relied on the use of the commercially available Josiphos **L4**, which moderately delivered the desired enantioenriched product **38** (Scheme 21). However, this catalytic system mainly gave the protodemetalation byproduct **39**, already observed in the previ-

our project. We decided to optimize the ligand structure by introducing various phosphines in the hope of improving the ee and the product distribution. Although previously reported, synthesis of these ligands was time-consuming, requiring six linear steps from ferrocene (Scheme 21A), and the evaluation of ligands **L5–L7** did not lead to any substantial improvement (Scheme 21B), although their purification by column chromatography was incredibly artistic. During one of our weekly updates, Jerome suggested that we try Ugi's amine intermediate **L1** directly as a ligand. Following the golden rule of 'it's faster to set up a reaction than to argue,' we skeptically tried it and, to our delight, we observed almost quantitative formation of product **38**, with complete suppression of the side protodemetalation. The reactivity issue was solved, but we still needed to improve the enantioselectivity. Aiming to achieve this goal, we varied the side alkyl chain of Ugi's amine ligand (**L8–L10**)²² and, after several attempts, we found that an isobutyl group provided the best results for this class of ligands; however, we could not improve further the reaction outcome, with only a small improvement over the pyrrolidine-containing ligand **L2** (Scheme 20).



After closing the chapter on ferrocene, we explored other ligand scaffolds. At some point, having an empty space in our heating blocks, we tested an old batch of DACH-Phenyl-Trost **L3**. We were not expecting good results from of this

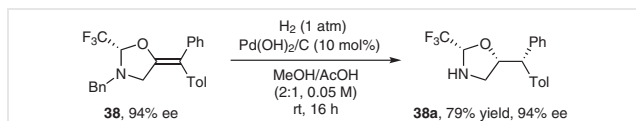
trial, because Trost ligands, despite being used in DYKATs, are commonly involved in palladium-catalyzed asymmetric allylation, where the palladium complex acts in close proximity to the stereocenter that is forged.^{2,14} Surprisingly, we obtained the desired product in 66% yield and 66% ee, surpassing all previously obtained results. It was time to start the 'ligand factory' again and to tune the structure of the Trost ligand to improve the results. Fortunately, these ligands are easily accessible, and their modular synthesis permits the rapid preparation of numerous analogues (Scheme 22A). We found that a huge batch of mono-Boc-protected cyclohexyldiamine **41** had been prepared (and chirally resolved) by Jerome in 2008 in one of his last ventures into the laboratory. This served as a precursor for the synthesis of the ligands. Having in mind the previous positive results with the P,N-ligands, we substituted the 2-(Ph₂P)-aryl fragment with a 2-pyridine (**L11**). This modification increased the ee to 79%, with a marginal effect on the yield (Scheme 22B). While evaluating the effect of this 'second arm' of the ligand, we synthesized the supposed-to-be monodentate **L12** and, for the third time in few months, we



were really surprised by the results. This ligand was capable of delivering the desired product in excellent yield and enantioselectivity. We could finally get an ee of over 90%, which is an important goal for researchers optimizing enantioselective transformations.

Further variations on the ligand structure did not significantly improve the reaction outcome (**L13** and **L14**). For these reasons, we selected **L12** as the best ligand for the enantioselective carboetherification and, to obtain a significant amount of it, we developed a cheaper and more practical synthetic route (Scheme 22C). A final tuning of the reaction conditions for the catalytic reaction allowed us to switch the solvent from DCE to diethyl ether and to reduce the temperature to 35 °C, obtaining the model product of the carboetherification **38** in >95% yield and 94% ee on a 0.4 mmol scale. The ‘few weeks’ had turned out to be almost forty.

Having access to the enantioenriched product **38**, we moved to an optimization of the diastereoselective catalytic hydrogenation. Due to its effectiveness in the reductive cleavage of C–N bond, we chose the Pearlman catalyst Pd(OH)₂/C,²³ aiming to obtain the reduced and deprotected product **39** in a single step. After a short screening of conditions, we found that a 2:1 mixture of methanol and acetic acid was the optimal solvent system for avoiding the catalyst poisoning, and we obtained the desired product in good yield and without any erosion of the optical purity (Scheme 23). We were finally ready to explore the scope of the process.

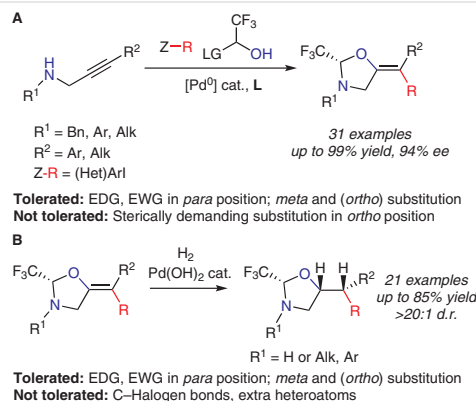


Scheme 23 Optimized condition for the diastereoselective hydrogenation of **38**.

Mikus: After fruitful undergraduate research in Riga Technical University, I was up for the challenge of a Ph.D. in organic chemistry. Recommended by Professor Turks, the Waser group was a good fit, with its unconventional approach to synthetic problems. Since my arrival to the LCSO group in September 2019, I had been working with Luca on the tethered enantioselective carboetherification of propargylic amines. In the initial plan, the project was expected to be finished within three to four months. However, I had already learned the reality of research during my master's studies; projects take more time than expected, even if you have already considered this fact. In the first three months, in a control experiment the ‘one-arm’ Trost ligand was found, the fine-tuning of the reaction conditions was finished, and the exploration of the scope could start.

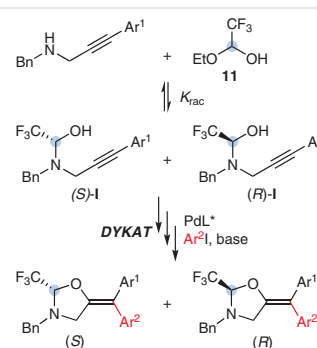
As a neophyte in asymmetric catalysis, at first it was frustrating to set up each substrate twice: an enantioenriched and a racemic variant. Moreover, due to the nature of

the two-step synthetic strategy, the rate of new entries was again halved. Nevertheless, it turned out to be an ‘easy’ scope study, with the majority of experiments giving good results (Scheme 24A). We were more concerned about the second step, as we did not know at the time whether the stereoselective hydrogenation would be general. Fortunately, we always obtained a single diastereoisomer of the reduced products (Scheme 24B). At this point, the COVID-19 pandemic situation in Switzerland and elsewhere was worsening by the hour. With the end of laboratory work within reach (with an expected one month or so left), EPFL went into full lockdown. The last day at the laboratory was particularly grim; Luca suggested preparing drinking-water reserves, in case the doomsday clock hit midnight. After six weeks of complete isolation, we returned part-time to the lab with unprecedented efficiency at the bench due to the limited working time. Finally, after six more weeks of partial occupation, things could go back to the new ‘normal’, and we were able to finish all of the experiments required for the project.



Scheme 24 Scope of the tethered enantioselective carboetherification of propargylic amines

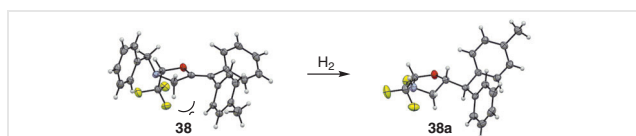
The mechanism and the model for asymmetric induction of the enantioselective carboetherification reaction remains highly speculative (Scheme 25). We know from NMR



Scheme 25 Equilibrium at the basis of the DYKAT

experiments that an equilibrium exists between the propargylic amine/hemiacetal **11** and the hemiaminal **I**. The constant racemization of hemiaminal **I**, combined with a discrimination between the two enantiomers by a chiral Pd catalyst, enables a DYKAT. However, the exact missing pieces of the puzzle are unknown, as was correctly pointed out by the committee of my candidacy examination.

We found the stereoselectivity of the hydrogenation particularly fascinating. The single-crystal X-ray structures of oxazolidine **38** and the reduced oxazolidine **38a** (Scheme 26) confirmed both the retention of the absolute configuration, and the approach of hydrogen from the opposite side from the CF₃ group. This was a relief, as the contrary would not be the first time in organic chemistry that the initial hypothesis would later be found to be far from reality.



Scheme 26 Rationalization of the site-selectivity in the hydrogenation of **38** based on its crystal structure

In fact, the installed CF₃-group on the oxazolidine **38** was acting as a *de facto* chiral auxiliary. To the best of our knowledge, the concept of a catalytically formed chiral auxiliary starting from nonchiral starting materials had never been reported in the literature. We feel our approach addresses many issues associated with the use of chiral auxiliaries, and more developments are expected in the future.

7 Conclusions (Jerome Waser)

It has been a privilege for me to work with three generations of talented young scientists on palladium catalysis. The fourth generation just entered the game, and I am sure that further exciting results can be expected. The surprise for me was, perhaps, that part of the initial project based on hypervalent iodine chemistry for oxyalkynylation could indeed be realized, even if no enantioselective methods could be developed at the time. It is always beautiful to see design become reality. This project brought many satisfactions, but also had its share of frustrations and tough decisions to take. We had to abandon our beloved hypervalent iodine reagents when they reached their limits. We were unable to develop general intermolecular transformations, but this forced us to adapt and to develop our new tether methodology, which led finally to success in enantioselective catalysis 12 years after the start of the project. At the beginning, there was some design, but the final success came out of pure serendipity: a control experiment that led to the discovery of the truncated Trost ligand **L12**. Success has outpaced understanding, and it will be highly interesting to in-

vestigate the mechanism and mode of stereoselection for this new DYKAT process. Progress is now in the hands of the next generation of researchers in the laboratory, and nobody can tell what the future will bring us!

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