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# Academia / Industry Collaborations Towards the Functionalization of Aryl Azoles

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*Abstract:* Aryl azoles can be found in numerous active pharmaceutical ingredients (APIs). Milvexian is a Factor XIa inhibitor currently in phase III for the treatment of thrombotic events containing an *ortho*-substituted 1-aryl-1*H*-1,2,3-triazole moiety. During the process development of Milvexian, we assessed multiple approaches for the preparation of 4-chloro-1,2,3-triazole, intermediate **1**. In this review article, we will detail how we initiated several academic collaborations to speed up the selection of the best synthesis for commercial manufacturing. Ultimately, those results not only helped us to achieve our goal but yielded general methodologies for the functionalization of azoles that extended even beyond our initial scope.

**Keywords:** Aryl azoles · Metalation · Milvexian · Triazoles

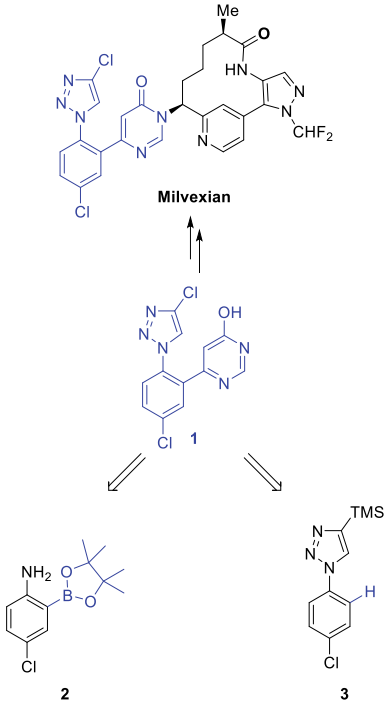
***Simon Wagschal*** earned his PhD in 2010 from École Polytechnique, Paris, France, under the supervision of Prof. El Kaïm and Prof. Grimaud. After a postdoctoral stay with Prof. Kündig in Geneva, Switzerland, he joined Janssen's Chemical Process R&D group in 2013. Since then, Simon has been involved in a dozen late-stage projects, developing and introducing new processes in the pilot and production plants. He received the Vice Presidents' Research Award for Outstanding Technical Achievement in 2020. In 2021, Simon joined the Janssen External R&D team, focusing on compounds in early development and delivering GxP batches at external partners. In 2023, Simon joined Lonza's Advanced Chemistry Technologies team.

***Diego Broggini*** earned his PhD in 2003 from ETH Zurich, Switzerland, under the supervision of Prof. Togni. After two postdoctoral stays with Prof. Lipshutz in Santa Barbara, US, and Prof. Altmann at ETH Zurich, Switzerland, he joined Janssen's Chemical Process R&D group in 2005. In the past 18 years at Janssen, Diego has been involved in the synthesis and process development of multiple drug candidates including three marketed drugs: Bedaquiline, Canagliflozin, and Erdafitinib. Most recently Diego has been developing into the CMC leader role.

## 1. Introduction

Milvexian is a Factor XIa (FXIa) inhibitor (Scheme 1), that has recently entered Phase III clinical trials.[1,2] In the past few years, our team has reported our various attempts towards the synthesis of 4-chloro-1,2,3-triazole **1** and the identification of an improved process for the preparation of this key Milvexian intermediate.

In this review, we intend to summarize such efforts with a focus on the various academic collaborations we leveraged to attain our goal. We will first cover the efforts towards the optimization of the preparation of compound **1** from boronic ester **2**.




Scheme 1. Raw materials tested for the preparation of compound **1**, a key intermediate in the synthesis of Milvexian.

In collaboration with Prof. Grimaud, we studied the mechanism of the Suzuki-Miyaura cross-coupling transmetalation step with diphosphines, which allowed us to develop a very robust process applicable to clinical supplies. In the second part of this review, we will summarize the results obtained for a direct late-stage *ortho*-functionalization of compound **3**, in collaborations with Prof. Ackermann and Prof. Knochel, resulting in the development of multiple broadly applicable methodologies extending beyond the preparation of aryl azoles.

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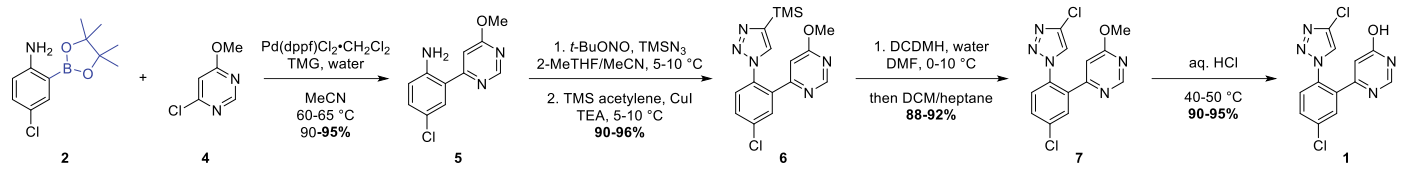



Scheme 2. Optimized medicinal chemistry route demonstrated on multi-hundred kg scale for compound **1**. TMG: 1,1,3,3-tetramethylguanidine. DCDMH: 1,3-dichloro-5,5-dimethylhydantoin.

## 2. Optimization and Scale-Up of the Initial FXIa Side Chain Route for Clinical Supply

The optimized conditions applied to the initial synthesis of intermediate **1** are summarized in Scheme 2.[3] This route was used to deliver suitable quantities of intermediate **1** for clinical supplies. We first optimized the Suzuki-Miyaura cross-coupling between **2** and **4** (Scheme 2) and found that the conversion profiles were more reproducible in acetonitrile. Kinetic studies on this step using the variable time normalization analysis (VTNA) approach[4] confirmed the robustness of the catalytic system based on the dppf ligand. Running this step in acetonitrile also offered the opportunity for a direct isolation of **5** by addition of water to the reaction mixture and filtration. We then improved the isolation of 4-trimethylsilyl-1,2,3-triazole **6** after the azidation-click sequence by crystallization from the reaction solvent – MeTHF – and heptane as an anti-solvent and avoiding methyl *tert*-butyl ether (MTBE), an additional solvent in which **6** was highly soluble. Direct isolations from the reaction mixture were also developed for the chlorination and demethylation steps, which reduced the waste generated by 75%. We also demonstrated that the recrystallization of the penultimate intermediate **7** was critical to control the purity and the color of the desired 4-chloro-1,2,3-triazole **1**, which could be obtained in 70% yield over five steps in the plant.

## 3. Role of dppf Monoxide in the Transmetalation Step of the Suzuki–Miyaura Cross-Coupling Reaction

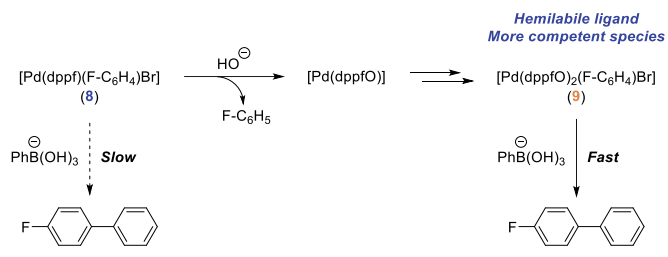
The key step in the sequence described in Scheme 2 was the Pd(dppf)$Cl_2$-mediated Suzuki-Miyaura cross-coupling between compounds **2** and **4**. While the transmetalation step of the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction has been studied extensively with monophosphines, the role of diphosphines (such as 1,1′-bis(diphenylphosphino)ferrocene (dppf), 1,3-bis(diphenylphosphino)propane (dppp) and 1,2-bis(diphenylphosphino)ethane (dppe)) in the boron-to-palladium transmetalation had not been firmly addressed. As part of our long-term collaboration with Dr. Laurence Grimaud,[5] we combined NMR spectroscopy, electrochemistry, and density functional theory (DFT) calculations to elucidate the role of dppf in this key elementary step of the Suzuki-Miyaura reaction.[6]

We found that dppf ligated to the oxidative addition complex **8** and could be oxidized *in situ* in the presence of base, leading to a dppfO-ligated palladium(0) complex. This dppfO palladium(0) complex can react further to form dppfO-ligated arylpalladium(II) complex **9** (Scheme 3). Complex **9**, thanks to the presence of the hemilabile ligand dppfO, is a more competent species in the subsequent transmetalation step, which occurs at room temperature (Scheme 4).

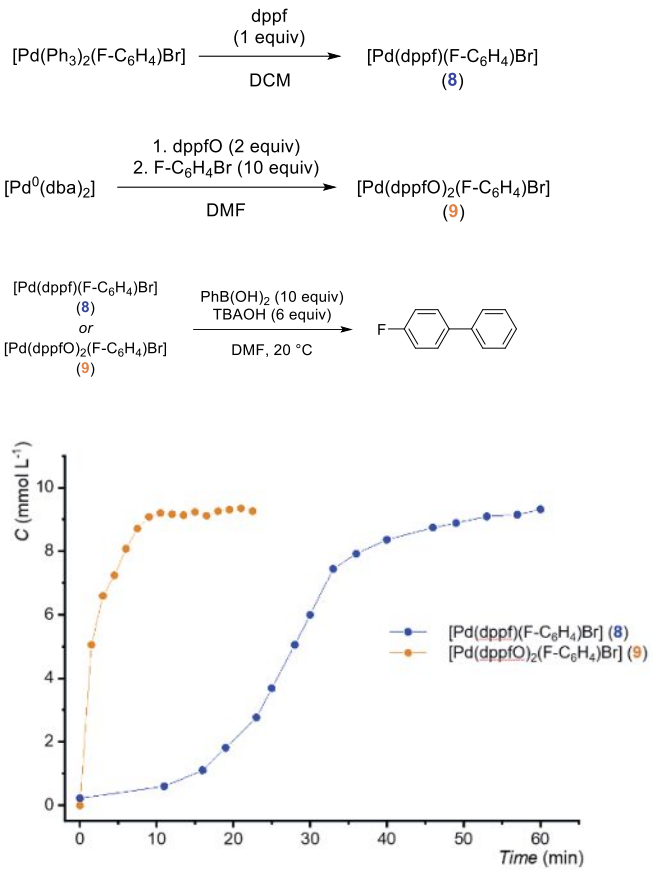
This was demonstrated by submitting the oxidation addition complexes **8** and **9** (prepared following the procedures described in Scheme 4) to the Suzuki-Miyaura conditions in the presence of a large excess of $PhB(OH)_2$ and base. The oxidative addition complex **9**, formed by reaction of [Pd(dba)$_2$] with dppfO in DMF, followed by treatment with arylbromide, is significantly faster than complex **8** in the transmetalation step, showing no activation time in the reaction profile (Scheme 4).

We also demonstrated that an excess of dppf would inhibit transmetalation involving the boronic acid and dppf-ligated arylpalladium(II) complex **8**, while an optimal [base]/[boronic acid] ratio maximized the concentration of a [Pd–O–B] key intermediate.

The Suzuki-Miyaura cross-coupling reaction described above proved to be robust and allowed us to produce sufficient amounts of supplies of compound **1**. However, the pre-functionalization of the aniline to a boronic ester was an expensive transformation that needed to be removed from the final sequence. With that in mind,




Scheme 3. Role of dppf monoxide in the transmetalation step of the Suzuki–Miyaura cross-coupling reaction.

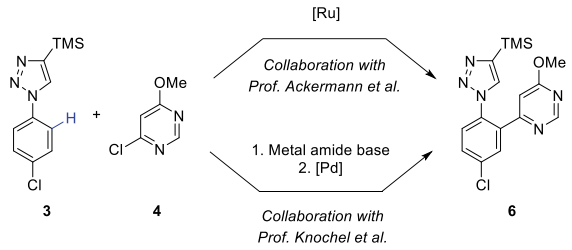



Scheme 4. Synthesis of complex **8** and **9** and monitoring of the formation of 4-fluoro-1,1′-biphenyl from **8** (blue) and **9** (orange) by $^{19}F\{^1H\}$ NMR.

we started investigating the direct late-stage *ortho*-functionalization of compound **3**.

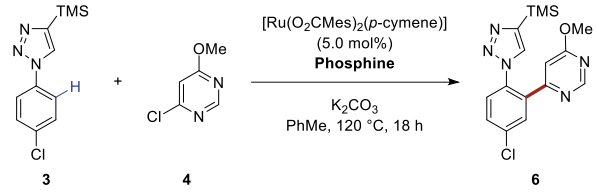
## 4. Triazole-Enabled Ruthenium (II) Carboxylate-Catalyzed C-H Arylation

To overcome the necessity of substrates pre-functionalized at the *ortho* position, we identified early on two alternative approaches relying on 4-TMS-1,2,3-triazole **3**, derived from 4-chloro aniline (Scheme 5). A first option would rely on a ruthenium-catalyzed C-H activation (top arrow), while the second would involve a regioselective metalation of aryl azole **3** followed by a Pd-catalyzed cross-coupling (bottom arrow).




Scheme 5. Two options considered for a direct C-H activation/functionalization of triazole **3**.

We surmised that the 1,2,3-triazole unit could act as a directing group, based on previous reports from Prof. Ackermann's and Larrossa's group using readily available and less expensive ruthenium catalysts.[7,8,9] The direct cross-coupling of **3** with chloropyrimidine **4** was studied in collaboration with the Ackermann group. Chloro-pyrimidine **4** turned out to be a difficult substrate in this transformation, requiring an electron-poor phosphine and affording a moderate yield of 50% (Scheme 6).[10]



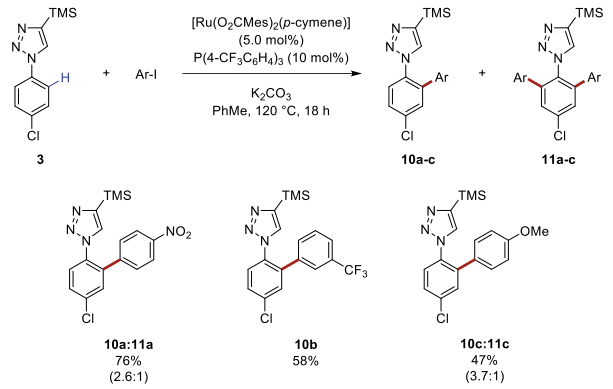

| *Phosphine* | Yield [%] |
|---|---|
| no ligand | 12 |
| $PCy_3$ (10 mol%) | n.r. |
| $PPh_3$ (10 mol%) | 21 |
| **$P(4\text{-}CF_3C_6H_4)_3$ (5 mol%)** | 50 |

Scheme 6. Ru-catalyzed C-H activation of compound **3** to obtain compound **6**.

The yield of this transformation could be improved up to 76% with other electron-deficient aryl iodides by using 10 mol% $P(4\text{-}CF_3C_6H_4)_3$. In some cases, the product **10** was isolated with the double arylation byproduct **11** (Scheme 7).

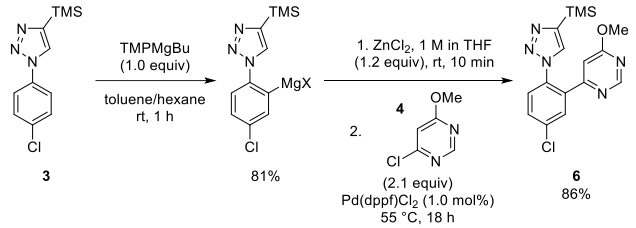
## 5. Regioselective Magnesiation and Functionalization of Aryl Azoles using a Tailored Amide Base

To further improve the access to aryl azole **6** and in collaboration with the group of Prof. Knochel, we investigated the metalation of 1-aryl-1*H*-1,2,3-triazole **3** and other related heterocycles with sterically hindered metal-amide bases.[11] We discovered a room temperature and highly regioselective *ortho*-magnesiation




Scheme 7. Ruthenium-catalyzed C-H arylation of compound **3** with alternative aryl iodides.

of several aryl azoles using a tailored magnesium amide, TMP-MgBu (TMP = 2,2,6,6-tetramethylpiperidyl) in hydrocarbon solvents followed by an efficient Pd-catalyzed arylation, delivering compound **6** in 70% yield over two steps (Scheme 8).




Scheme 8. Metalation/Pd-catalyzed Negishi cross-coupling sequence of **3** to Milvexian intermediate **6**.

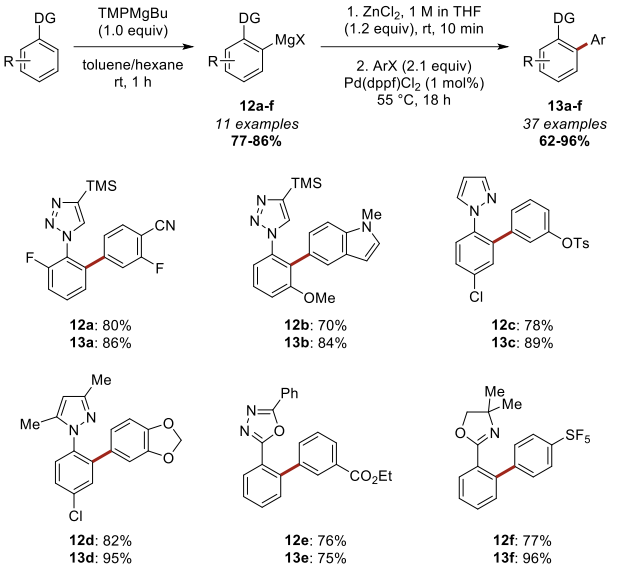
This scalable and selective reaction allowed variation of the initial substitution pattern of the aryl ring, the nature of the azole moiety that would serve as a directing group (DG), as well as the nature of the electrophile (Scheme 9).

## 6. *s*$Bu_2$Mg as a Regioselective *ortho, ortho'*-Magnesiation Reagent of Aromatics and Heterocycles

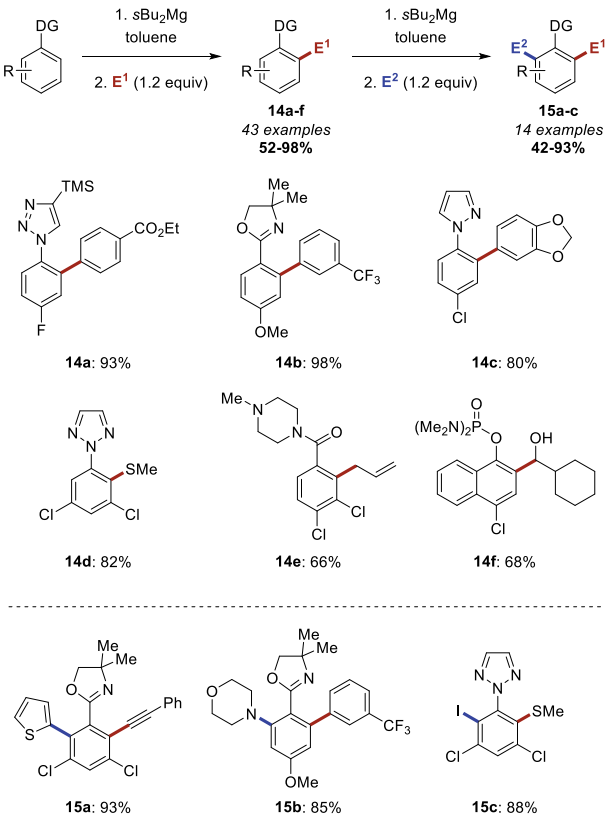
The drawbacks of the TMPMgBu methodology were the price and availability of the TMP-H amine but also the large excess of electrophile required, resulting in the Ar-*n*Bu impurity. We recently showed that *s*$Bu_2$Mg was an improved magnesiation reagent, which allowed a highly *ortho*-regioselective magnesiation of arenes bearing various DGs, leading after trapping of the resulting diarylmagnesium species with various electrophiles $E^1$ to products of type **14** (Scheme 10). These polyfunctional arenes were in several cases magnesiated again using *s*$Bu_2$Mg producing, after addition of a second electrophile $E^2$, valuable 1,2,3-polyfunctional arenes of type **15**.[12]

## 7. Conclusion

During the development of a process route towards the side chain **1** of Milvexian, we teamed up with several academic groups to leverage their own unique expertise. The collaboration with the team of Prof. Grimaud helped us to understand how to best perform the Suzuki-Miyaura cross-coupling, allowing us to develop a very robust process capable of supplying the necessary amounts of drug substance for clinical supplies. In parallel, the studies performed in collaboration with the Ackermann and Knochel research groups culminated in the identification of a cost-effective and convergent synthesis of key intermediate **6**, avoiding both the




Scheme 9. Extension of the TMPMgBu methodology to aryl pyrazoles, 1,3,4-oxadiazoles and oxazolines.




Scheme 10. Regioselective magnesiation and *ortho*, *ortho*'-functionalization of arenes and heteroarenes using $sBu_2Mg$ in toluene.

need for bromination and borylation. Additionally, we could expand the reaction of interest and develop two general methodologies that are broadly applicable to a wide range of substrates that extend beyond aryl azoles. We are convinced that strong and close collaborations between industry and academia are paramount to quickly identifying the best route for process development but also to provide new methodologies for medicinal chemists to explore chemical space.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