

Progress of the Suzuki-Miyaura Reaction

叶青杨 3210100360

(Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang, 310058)

Abstract Due to cheapness and earth abundance, the Suzuki-Miyaura cross-coupling reaction has gradually shifted from mainly using the traditional Pd metal to using the more attractive first-row transition metal Ni in recent years. In this review, we briefly summarize some progress in Pd and Ni catalyzed Suzuki-Miyaura reactions.

Keywords Suzuki-Miyaura Reaction; C-C Coupling; Abundant Transition Metals; Pd Catalyst; Ni Catalyst

1 Introduction

In organometallic chemistry, coupling reactions related to the formation of carbon-carbon single bonds are particularly noteworthy. The Suzuki-Miyaura reaction, as an important one among them, has developed very rapidly in recent years. In this review, we will provide a systematic introduction to the Suzuki-Miyaura reaction catalyzed by Pd and Ni.

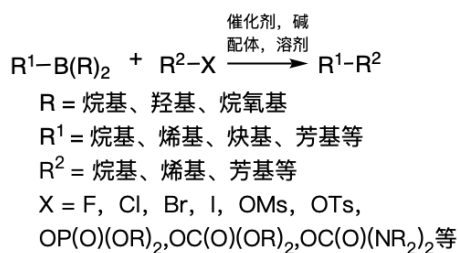


Figure 1: Typical Conditions for the Suzuki-Miyaura Cross-Coupling Reaction

The Suzuki-Miyaura reaction is commonly defined as a reaction forming carbon-carbon bonds between organoboron compounds and organic halides or pseudo-halides, such as sulfonates, phosphates, carbonates, etc., under the action of transition metals like palladium or nickel, as shown in Figure 1. This reaction was first reported in 1979 by the Japanese organic chemists A. Suzuki and N. Miyaura. The appeal of this reaction lies in its mild reaction conditions, broad functional group tolerance, and good stereo- and regioselectivity. Organoboron reagents are readily available and have considerable stability against air and moisture. Moreover, the boronic acid by-products of the reaction are usually less toxic or even non-toxic and easily separable due to their water solubility. Thus, upon its discovery, it quickly became an attractive solution for many organic syntheses.^{1,2}

As shown in Figure 2, the mechanism of the Suzuki-Miyaura reaction usually follows an M⁽⁰⁾/M^(II) mechanism. The active catalytic intermediate, a zero-valent transition metal complex M₁⁽⁰⁾ compound A, is obtained by reducing the initial divalent transition metal M₁^(II) complex. Compound A undergoes oxidative addition with organic halides or pseudo-halides to form an M₁^(II) intermediate B. X⁻ in B can exchange with Y⁻ to form C, and B or C undergoes transmetalation to form D. Finally, a reductive elimination reaction occurs, producing the product and regenerating the zero-valent M₁⁽⁰⁾ complex A, completing the catalytic cycle. The oxidative addition of the halide is the rate-determining step, and the reaction rate typically follows I ≫ Br > OTf ≫ Cl.³

Many studies have found that under certain conditions, by adjusting the structural properties of ligands, Ni catalysts can catalyze the Suzuki-Miyaura reaction via a $\text{Ni}^{\text{I}}/\text{Ni}^{\text{III}}$ process, but its mechanism differs from that shown in Figure 2, as illustrated in Figure 3. The zero-valent nickel complex undergoes a single electron transfer reaction to form the Ni^{I} intermediate E. E undergoes transmetalation to form the Ni^{II} intermediate F. F continues to undergo oxidative addition with the halide to yield the Ni^{III} intermediate G. Finally, after a reductive elimination, the product is formed and the Ni^{I} complex E is regenerated, completing the catalytic cycle of the reaction.

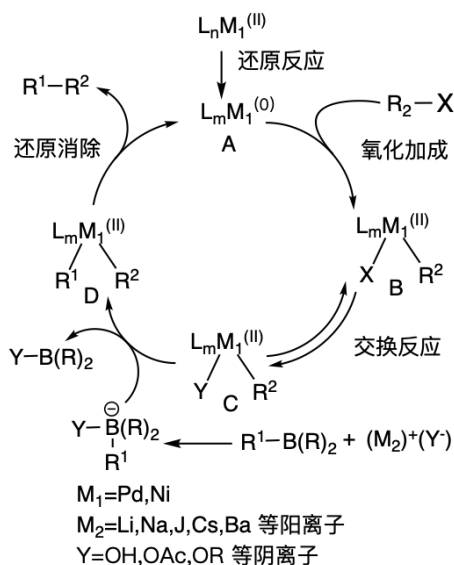


Figure 2: Common Mechanism of the Suzuki-Miyaura Cross-Coupling Reaction

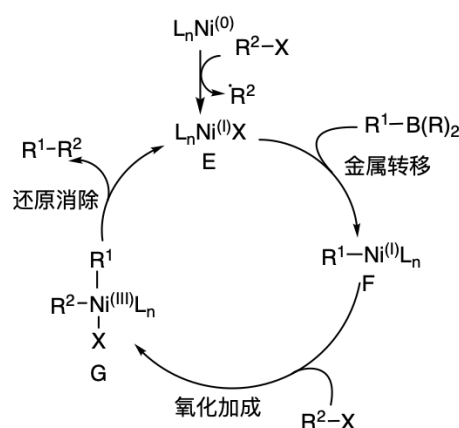


Figure 3: The $\text{Ni}^{\text{I}}/\text{Ni}^{\text{III}}$ Mechanism of the Suzuki-Miyaura Cross-Coupling Reaction

2 Pd-Catalyzed Suzuki-Miyaura Reaction

2.1 Reaction Examples Using 9-BBN⁴

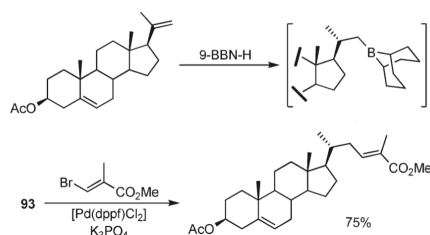


Figure 4: Suzuki-Miyaura Coupling Reaction with Steroidal Moiety⁵

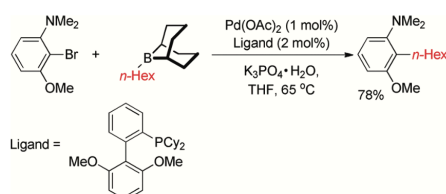


Figure 5: Suzuki-Miyaura Coupling Reaction with Electron-Rich, Hindered Aryl Bromides⁶

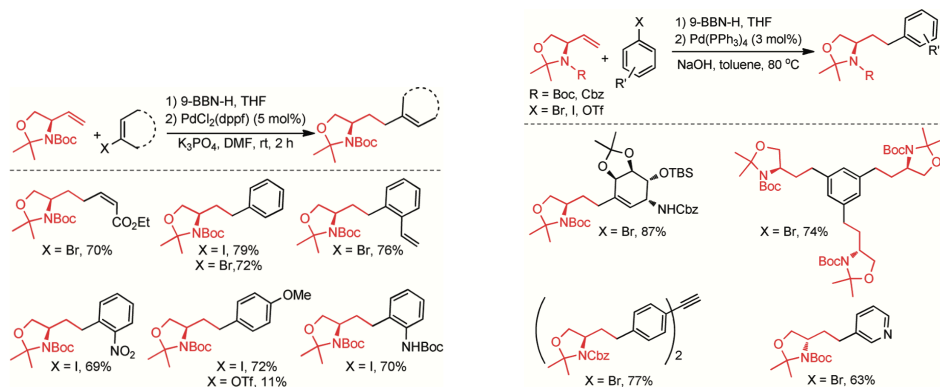


Figure 6: Application of the Suzuki-Miyaura Coupling Reaction in Amino Acid Synthesis⁷ Figure 7: Application of the Suzuki-Miyaura Coupling Reaction in Amino Acid Synthesis⁸

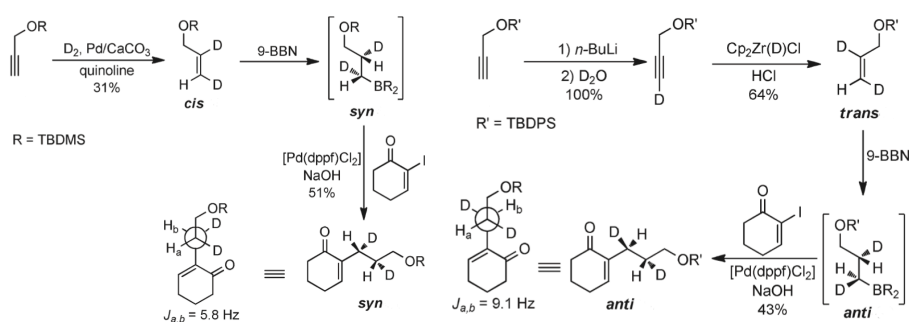


Figure 8: Chiral Chemistry of the Suzuki-Miyaura Coupling Reaction⁹

2.2 Reaction Examples with Phosphate Esters

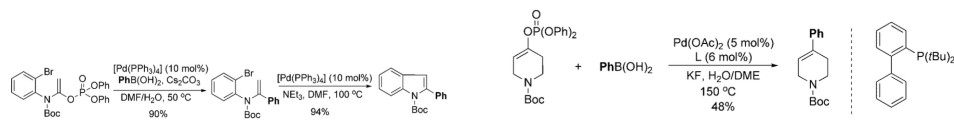


Figure 9: Suzuki-Miyaura Coupling Reaction with Vinyl Phosphate Esters¹⁰ Figure 10: Suzuki-Miyaura Coupling Reaction with Unactivated Vinyl Phosphate Esters¹¹

2.3 Reaction Examples with p-Toluenesulfonate Esters

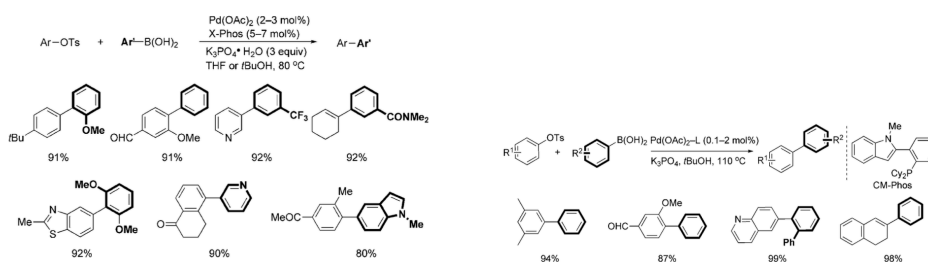


Figure 11: Suzuki-Miyaura Coupling Reaction with p-Toluenesulfonate Esters in the Presence of X-Phos¹² Figure 12: Suzuki-Miyaura Coupling Reaction with p-Toluenesulfonate Esters in the Presence of CM-Phos¹³

2.4 Reaction Examples with Methylsulfonate Esters

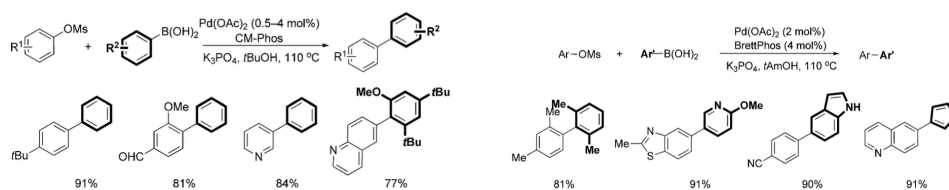


Figure 13: Suzuki-Miyaura Coupling Reaction with Methylsulfonate Esters in the Presence of CM-Phos¹⁴ Figure 14: Suzuki-Miyaura Coupling Reaction with Methylsulfonate Esters in the Presence of BrettPhos¹⁵

Examples of Pd-catalyzed Suzuki-Miyaura coupling reactions are fewer compared to those catalyzed by Ni, and in recent years, organic chemists have primarily focused their interest on the Suzuki-Miyaura coupling reactions involving Ni. Moreover, due to the limited studies on the mechanisms of Pd-catalyzed reactions and the narrow applicability for sp^3 -hybridized and bulky, non-activated sp^2 -hybridized halides/pseudo-halides, as well as related asymmetric coupling reactions, the scope remains somewhat limited. Consequently, in the research on Ni-catalyzed Suzuki-Miyaura coupling reactions, there are more examples.

3 Ni-Catalyzed Suzuki-Miyaura Reaction^{16,17}

3.1 Reaction Examples with Aryl Halides

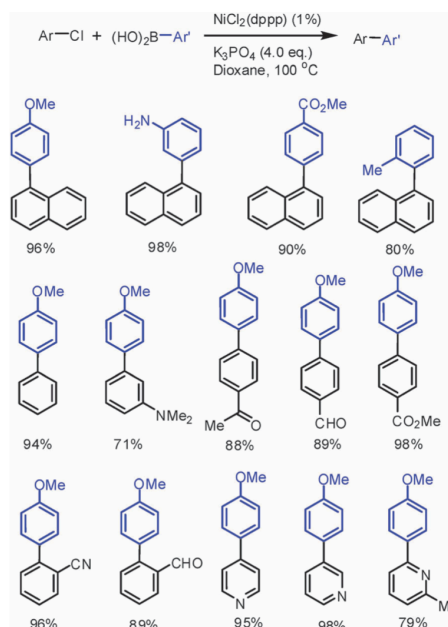
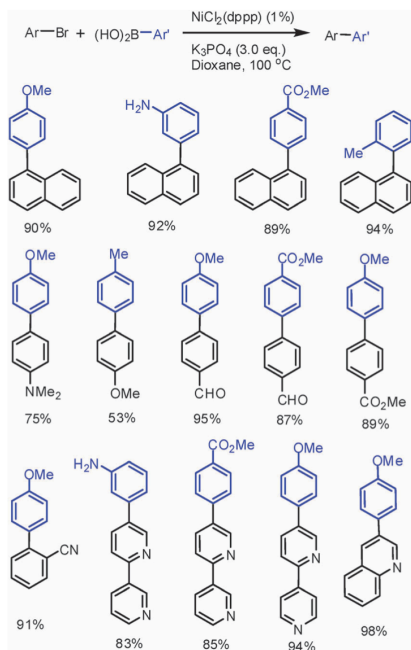


Figure 15: Suzuki-Miyaura Coupling Reaction with Aryl Bromides¹⁸ Figure 16: Suzuki-Miyaura Coupling Reaction with Aryl Chlorides¹⁸

3.2 Reaction Examples with Alkyl Halides

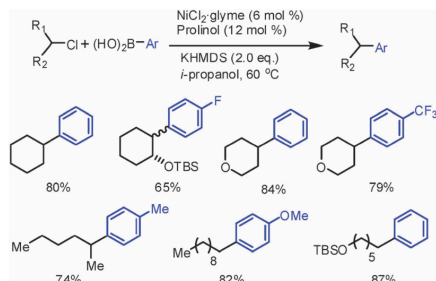


Figure 17: Suzuki-Miyaura Coupling Reaction with Alkyl Chlorides and Iodides¹⁹

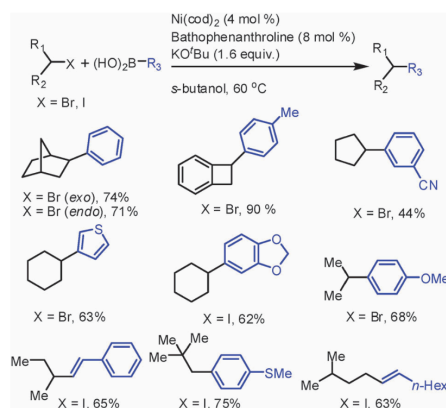


Figure 18: Suzuki-Miyaura Coupling Reaction with Alkyl Chlorides²⁰

3.3 Reaction Examples with Arylsulfonamides

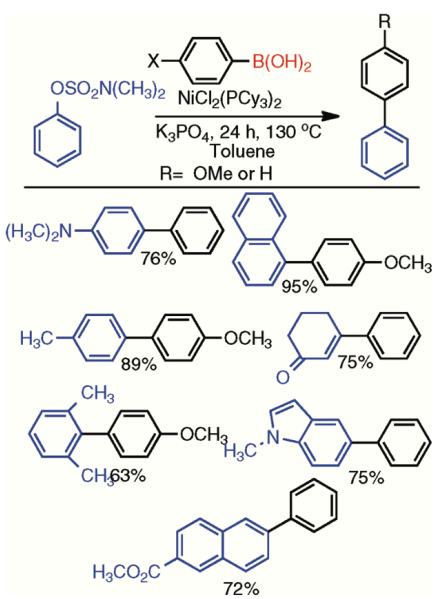


Figure 19: High-Yield Suzuki-Miyaura Coupling Reactions with Arylsulfonamides²¹

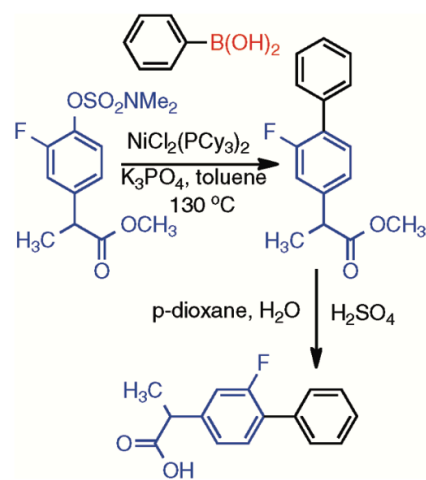


Figure 20: Examples of Suzuki-Miyaura Coupling Reactions with Arylsulfonamides in Synthesis (Flurbiprofen)²¹

3.4 Reaction Examples with Aryl Methyl Ethers

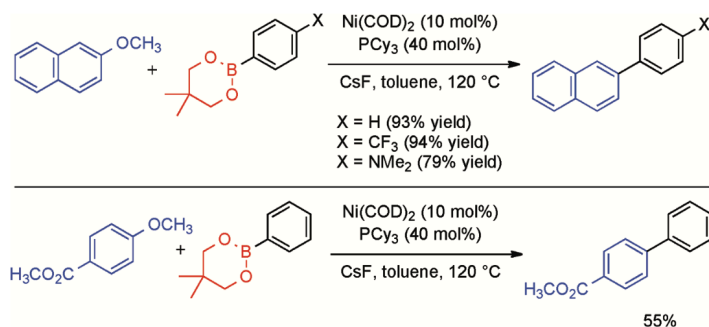


Figure 21: Suzuki-Miyaura Coupling Reaction with Aryl Methyl Ethers²²

3.5 Reaction Examples with Phosphate Esters

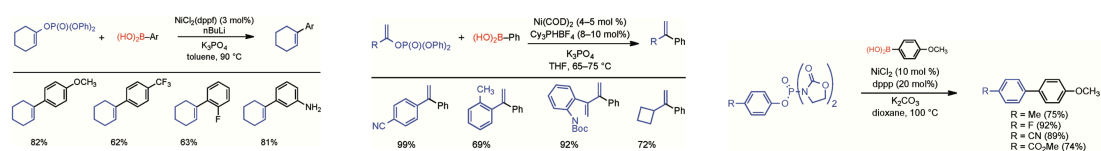


Figure 22: Suzuki-Miyaura Coupling Reaction with Phosphate Esters²³⁻²⁵

3.6 Reaction Examples with Aryl Carbonates

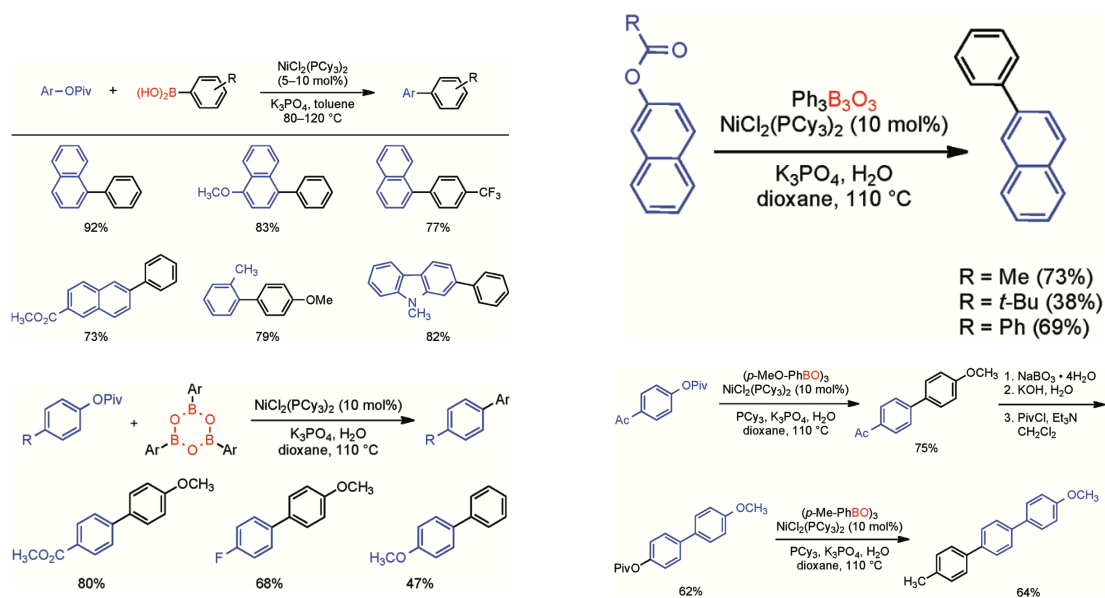


Figure 23: Suzuki-Miyaura Coupling Reaction with Aryl Carbonates²⁶⁻²⁸

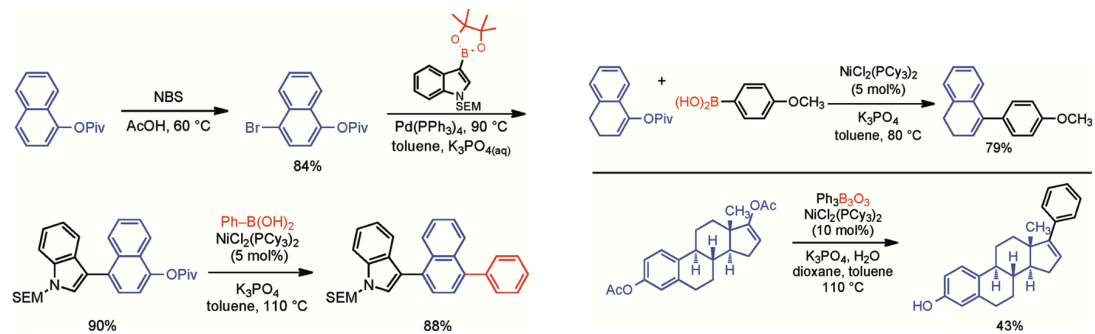


Figure 24: Examples of Suzuki-Miyaura Coupling Reactions with Aryl Carbonates in Synthesis^{26,29}

3.7 Reaction Examples with Aminosulfonate Esters

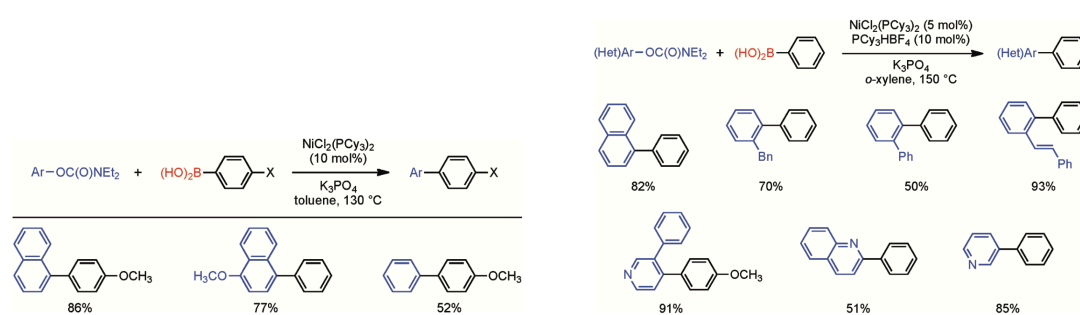


Figure 25: Examples of Suzuki-Miyaura Coupling Reactions with Carbamate Esters in Synthesis^{21,30}

3.8 Reaction Examples with Aminosulfonate Esters

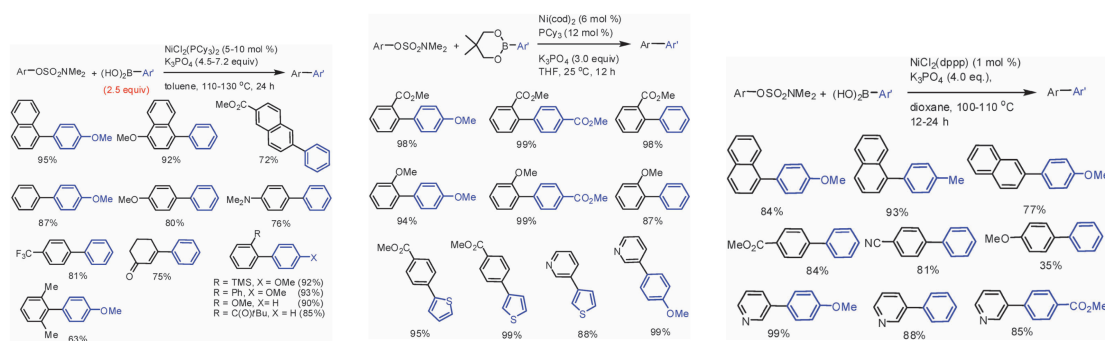


Figure 26: Suzuki-Miyaura Coupling Reactions of Aminosulfonate Esters under Various Ni Catalysts³¹⁻³³

3.9 Reaction Examples with Aryl Fluorides

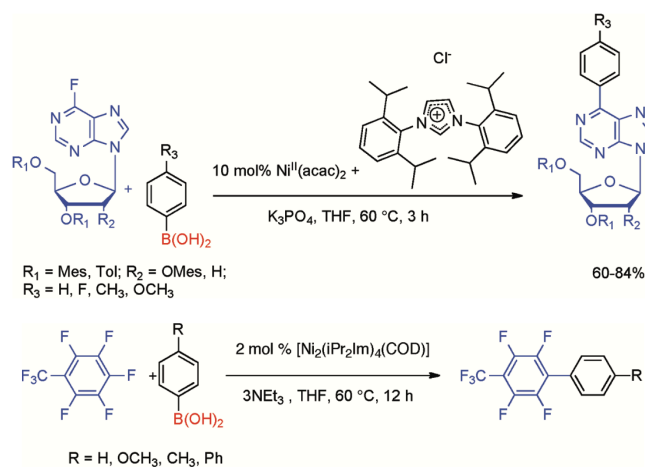


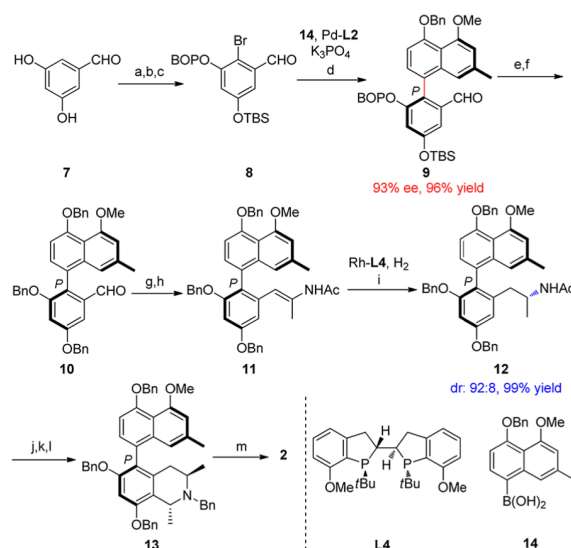
Figure 27: Suzuki-Miyaura Coupling Reaction with Aryl Fluorides^{33,34}

4 Application of Suzuki-Miyaura Coupling Reaction in the Total Synthesis of Complex Natural Products

In recent years, with the advancement of organic synthetic chemistry, more cutting-edge content in organometallic chemistry has been applied in practical synthesis. The Suzuki-Miyaura coupling reaction is playing an increasingly important role in the efficient total synthesis of many complex natural products.

In 2014, the research group led by Tang Wenjun³⁵ developed a mild and efficient method for asymmetric Suzuki-Miyaura cross-coupling reactions (Figure 28). Using a chiral catalyst system composed of $\text{Pd}(\text{OAc})_2$ and the chiral phosphine ligand **L2**, they achieved asymmetric cross-coupling of bulky aryl bromides with boronic acids. The reaction yielded P-configuration products with up to 96% yield and 93% ee. Through subsequent transformations using this intermediate, the first total synthesis of korupensamine A was realized. Similarly, using **ent-L2** as the chiral ligand, the corresponding M-configuration products were obtained with high enantioselectivity and yield, leading to the first total synthesis of korupensamine B. Later, the authors employed the Suzuki-Miyaura cross-coupling reaction to couple reaction intermediates, completing the efficient total synthesis of the polyaromatic natural product michellamine B.

4.1 Total Synthesis of korupensamine A, korupensamine B and michellamine B



Conditions: (a) TBSCl, TEA, DCM, -78 °C to rt, 59%; (b) NBS, DCM, -15 °C, 86%; (c) BOPCl, TEA, DCM, 98%; (d) **14**, Pd(OAc)₂/L2, K₃PO₄, toluene/H₂O = 5/1, 96%, 93% ee; (e) NaOH, MeOH, 97%; (f) BnBr, K₂CO₃, DMF, 95%; (g) EtNO₂, HO(CH₂)₂NH₃⁺HCO₂⁻, 60 °C, 92%; (h) Fe, AcOH, Ac₂O, DMF, 70 °C, 60%; (i) 1 mol % Rh(nbd)₂BF₄/L4, H₂ (20 atm), DCM, 0 °C, 12 h, 99%, d.r. 92/8; (j) BnBr, NaH, DMF, 96%; (k) POCl₃, 2,4,6-collidine, toluene, 100 °C, 4 h; (l) NaBH₄, EtOH, -78 °C to rt, 85% (over 2 steps, *trans:cis* = 6/1); (m) Pd/C (5%), H₂ (1 atm), MeOH/DCM = 2/1, 3 h, 95%.

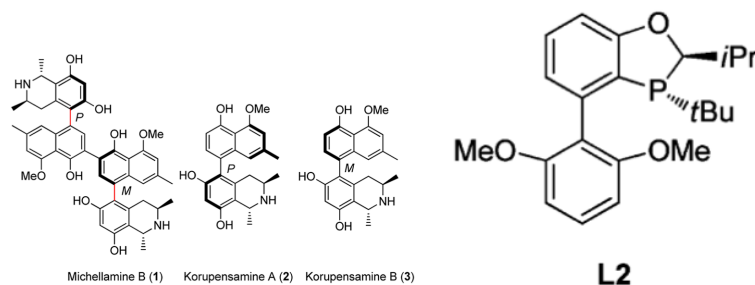


Figure 28: Total Synthesis of korupensamine A, korupensamine B, and michellamine B

4.2 Diverse Total Synthesis of Bird's Nest Alkane and Hamigeran Series of Natural Products

In 2018, the research group led by Han Fusha^{36,37} developed a new class of cyclic palladium catalysts based on phosphoramidite ligands. These catalysts exhibited high catalytic activity for Suzuki-Miyaura cross-coupling reactions between bulky, non-activated cyclic trifluoromethanesulfonate enol ester derivatives and arylboronic acids (esters). The reaction could proceed smoothly at room temperature. Additionally, this reaction demonstrated broad substrate adaptability, yielding high yields of coupled products for variously substituted five-membered, six-membered, and bridged ring enol derivatives. Further studies showed that this method played a decisive role in the straightforward, efficient, and diverse total synthesis of diterpene natural products, including the bird's nest alkane type and hamigeran.

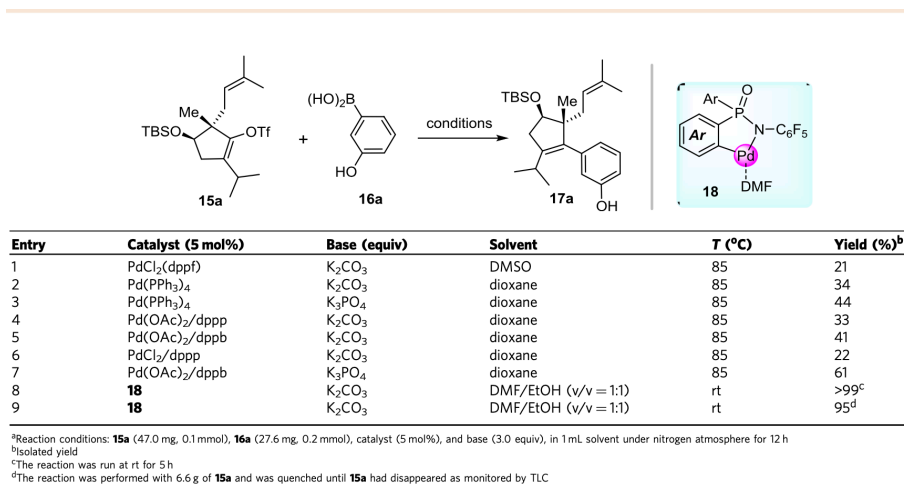


Figure 29: Condition Screening for the Synthesis of Key Intermediates

5 Conclusion and Outlook

In summary, this review has provided a comprehensive overview of the Suzuki-Miyaura cross-coupling reaction, focusing on the advancements and applications of both palladium- and nickel-catalyzed methods. The evolution of these reactions over recent years demonstrates their versatility and growing importance in the field of synthetic chemistry. Particular attention has been given to the nickel-catalyzed Suzuki-Miyaura reaction due to its increasing prominence and potential. The future of this methodology appears promising, with expectations of continued innovation and broader application in complex molecule synthesis. We anticipate further developments in this area, potentially leading to more efficient, sustainable, and cost-effective synthetic strategies.

References

- [1] Sherry R Chemler, Dirk Trauner, and Samuel J Danishefsky. The B-Alkyl Suzuki-Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis A list of abbreviations can be found at the end of the article. *Angew Chem Int Ed Engl*, 40(24):4544--4568, Dec 2001.
- [2] K C Nicolaou, Paul G Bulger, and David Sarlah. Palladium-catalyzed cross-coupling reactions in total synthesis. *Angew Chem Int Ed Engl*, 44(29):4442--4489, Jul 2005.
- [3] Adam F. Littke, Chaoyang Dai, and Gregory C. Fu. Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *Journal of the American Chemical Society*, 122(17):4020--4028, 05 2000.
- [4] Ranjan Jana, Tejas P. Pathak, and Matthew S. Sigman. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chemical Reviews*, 111(3):1417--1492, 03 2011.
- [5] Norio Miyaura, Tatsuo Ishiyama, Hirotomo Sasaki, Masako Ishikawa, Makoto Sato, and Akira Suzuki. Palladium-catalyzed inter- and intramolecular cross-coupling reactions of B-alkyl-9-borabicyclo[3.3.1]nonane derivatives with 1-halo-1-alkenes or haloarenes. Syntheses of functionalized alkenes, arenes, and cycloalkenes via a hydroboration-coupling sequence. *Journal of the American Chemical Society*, 111(1):314--321, 01 1989.
- [6] Shawn D. Walker, Timothy E. Barder, Joseph R. Martinelli, and Stephen L. Buchwald. A Rationally Designed Universal Catalyst for Suzuki--Miyaura Coupling Processes. *Angewandte Chemie International Edition*, 43(14):1871--1876, 2004.
- [7] Andrew D. Campbell, Tony M. Raynham, and Richard J.K. Taylor. The synthesis of novel amino acids via hydroboration-Suzuki cross coupling. *Tetrahedron Letters*, 40(28):5263--5266, 1999.
- [8] Mark Sabat and Carl R. Johnson. Synthesis of Unnatural Amino Acids via Suzuki Cross-Coupling of Enantiopure Vinyloxazolidine Derivatives. *Organic Letters*, 2(8):1089--1092, 04 2000.
- [9] Brian H. Ridgway and K. A. Woerpel. Transmetalation of Alkylboranes to Palladium in the Suzuki Coupling Reaction Proceeds with Retention of Stereochemistry. *The Journal of Organic Chemistry*, 63(3):458--460, 02 1998.
- [10] Haruhiko Fuwa, Akane Kaneko, Yasuaki Sugimoto, Taisuke Tomita, Takeshi Iwatsubo, and Makoto Sasaki. Concise and Short Synthesis of Functionalized 5,6-Dihydropyridin-2-ones by Means of Palladium(0)-Catalyzed Cross-Coupling of Ketene Amino Phosphates. *The Japan Institute of Heterocyclic Chemistry*, 70(1):101--106, 9 2006.
- [11] Uffe S. Larsen, Lars Martiny, and Mikael Begtrup. Synthesis of 4-substituted tetrahydropyridines by cross-coupling of enol phosphates. *Tetrahedron Letters*, 46(24):4261--4263, 2005.

- [12] Hanh Nho Nguyen, Xiaohua Huang, and Stephen L. Buchwald. The First General Palladium Catalyst for the Suzuki–Miyaura and Carbonyl Enolate Coupling of Aryl Arenesulfonates. *Journal of the American Chemical Society*, 125(39):11818--11819, 10 2003.
- [13] Chau Ming So, Chak Po Lau, Albert S. C. Chan, and Fuk Yee Kwong. Suzuki–Miyaura Coupling of Aryl Tosylates Catalyzed by an Array of Indolyl Phosphine–Palladium Catalysts. *The Journal of Organic Chemistry*, 73(19):7731--7734, 10 2008.
- [14] Chau Ming So, Chak Po Lau, and Fuk Yee Kwong. A General Palladium–Catalyzed Suzuki–Miyaura Coupling of Aryl Mesylates. *Angewandte Chemie International Edition*, 47(42):8059--8063, 2008.
- [15] Brijesh Bhayana, Brett P. Fors, and Stephen L. Buchwald. A Versatile Catalyst System for Suzuki–Miyaura Cross-Coupling Reactions of C(sp²)-Tosylates and Mesylates. *Organic Letters*, 11(17):3954--3957, 09 2009.
- [16] Brad M. Rosen, Kyle W. Quasdorf, Daniella A. Wilson, Na Zhang, Ana-Maria Resmerita, Neil K. Garg, and Virgil Percec. Nickel-catalyzed cross-couplings involving carbon–oxygen bonds. *Chemical Reviews*, 111(3):1346--1416, 03 2011.
- [17] Fu-She Han. Transition-metal-catalyzed Suzuki–Miyaura cross-coupling reactions: a remarkable advance from palladium to nickel catalysts. *Chem. Soc. Rev.*, 42:5270--5298, 2013.
- [18] Yu-Long Zhao, You Li, Shui-Ming Li, Yi-Guo Zhou, Feng-Yi Sun, Lian-Xun Gao, and Fu-She Han. A Highly Practical and Reliable Nickel Catalyst for Suzuki–Miyaura Coupling of Aryl Halides. *Advanced Synthesis & Catalysis*, 353(9):1543--1550, 2011.
- [19] Jianrong (Steve) Zhou and Gregory C. Fu. Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides. *Journal of the American Chemical Society*, 126(5):1340--1341, 02 2004.
- [20] Francisco González-Bobes and Gregory C. Fu. Amino Alcohols as Ligands for Nickel-Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids. *Journal of the American Chemical Society*, 128(16):5360--5361, 04 2006.
- [21] Kyle W. Quasdorf, Michelle Riener, Krastina V. Petrova, and Neil K. Garg. Suzuki–Miyaura Coupling of Aryl Carbamates, Carbonates, and Sulfamates. *Journal of the American Chemical Society*, 131(49):17748--17749, 12 2009.
- [22] Mamoru Tobisu, Toshiaki Shimasaki, and Naoto Chatani. Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters, url = <https://onlinelibrary.wiley.com/doi/abs/10.1002/anie.200801447>. *Angewandte Chemie International Edition*, 47(26):4866--4869, 2008.
- [23] Yang Nan and Zhen Yang. Nickel-catalyzed cross-couplings of cyclohexenyl phosphate and arylboronic acids. *Tetrahedron Letters*, 40(17):3321--3324, 1999.
- [24] Anders L. Hansen, Jean-Philippe Ebran, Thomas M. Gøgsig, and Troels Skrydstrup. Direct synthesis of 1,1-diarylalkenes from alkenyl phosphates via nickel(0)-catalysed Suzuki–Miyaura coupling. *Chem. Commun.*, pages 4137--4139, 2006.

- [25] Yu-Long Zhao, You Li, Yu Li, Lian-Xun Gao, and Fu-She Han. Aryl Phosphoramides: Useful Electrophiles for Suzuki–Miyaura Coupling Catalyzed by a NiCl₂/dppp System (dppp=1,3-Bis(diphenylphosphino)propane). *Chemistry -- A European Journal*, 16(17):4991--4994, 2010.
- [26] Kyle W. Quasdorf, Xia Tian, and Neil K. Garg. Cross-Coupling Reactions of Aryl Pivalates with Boronic Acids. *Journal of the American Chemical Society*, 130(44):14422--14423, 11 2008.
- [27] Bing-Tao Guan, Yang Wang, Bi-Jie Li, Da-Gang Yu, and Zhang-Jie Shi. Biaryl Construction via Ni-Catalyzed C–O Activation of Phenolic Carboxylates. *Journal of the American Chemical Society*, 130(44):14468--14470, 11 2008.
- [28] Lukas J. Gooßen, Käthe Gooßen, and Corneliu Stanciu. C(aryl)-O Activation of Aryl Carboxylates in Nickel-Catalyzed Biaryl Syntheses. *Angewandte Chemie International Edition*, 48(20):3569--3571, 2009.
- [29] Chang-Liang Sun, Yang Wang, Xiao Zhou, Zhen-Hua Wu, Bi-Jie Li, Bing-Tao Guan, and Zhang-Jie Shi. Construction of Polysubstituted Olefins through Ni-Catalyzed Direct Activation of Alkenyl C–O of Substituted Alkenyl Acetates. *Chemistry -- A European Journal*, 16(20):5844--5847, 2010.
- [30] Aurora Antoft-Finch, Tom Blackburn, and Victor Snieckus. N,N-Diethyl O-Carbamate: Directed Metalation Group and Orthogonal Suzuki–Miyaura Cross-Coupling Partner. *Journal of the American Chemical Society*, 131(49):17750--17752, 12 2009.
- [31] Kyle W. Quasdorf, Michelle Riener, Krastina V. Petrova, and Neil K. Garg. Suzuki–Miyaura Coupling of Aryl Carbamates, Carbonates, and Sulfamates, type = doi: 10.1021/ja906477r. *Journal of the American Chemical Society*, 131(49):17748--17749, 12 2009.
- [32] Pawaret Leowanawat, Na Zhang, Ana-Maria Resmerita, Brad M. Rosen, and Virgil Percec. Ni(COD)₂/PCy₃ Catalyzed Cross-Coupling of Aryl and Heteroaryl Neopentylglycolboronates with Aryl and Heteroaryl Mesylates and Sulfamates in THF at Room Temperature. *The Journal of Organic Chemistry*, 76(24):9946--9955, 12 2011.
- [33] Guo-Jun Chen and Fu-She Han. An Efficient Suzuki–Miyaura Coupling of Aryl Sulfamates and Boronic Acids Catalyzed by NiCl₂(dppp). *European Journal of Organic Chemistry*, 2012(19):3575--3579, 2012.
- [34] Thomas Schaub and Udo Radius. Efficient C-F and C-C Activation by a Novel N-Heterocyclic Carbene--Nickel(0) Complex. *Chemistry -- A European Journal*, 11(17):5024--5030, 2005.
- [35] Guangqing Xu, Wenzhen Fu, Guodu Liu, Chris H. Senanayake, and Wenjun Tang. Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki–Miyaura Coupling Reactions. *Journal of the American Chemical Society*, 136(2):570--573, 01 2014.
- [36] Guo-Jie Wu, Yuan-He Zhang, Dong-Xing Tan, and Fu-She Han. Total synthesis of cyrneines A--B and glaucopine C. *Nature Communications*, 9(1):2148, 2018.
- [37] Bao-Chen Cao, Guo-Jie Wu, Fang Yu, Yu-Peng He, and Fu-She Han. A Total Synthesis of (–)-Hamigeran B and (–)-4-Bromohamigeran B. *Organic Letters*, 20(12):3687--3690, 06 2018.