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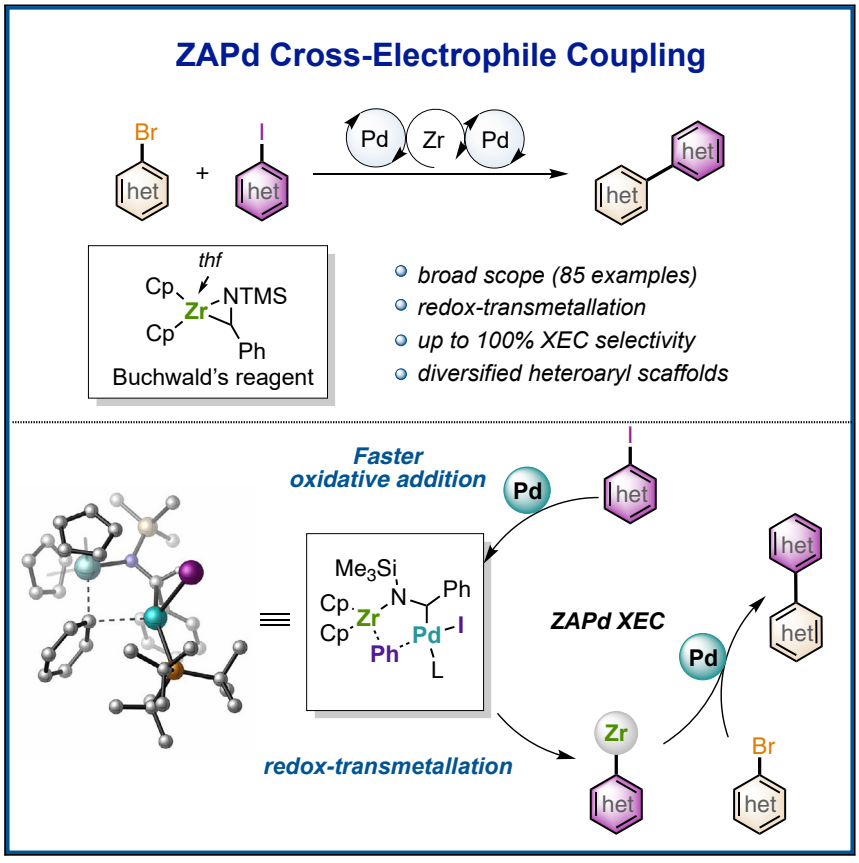

Heterocycles are ubiquitous in bioactive molecules. The construction of heteroaromatic scaffolds, which mainly relies on classical cross-coupling reactions, remains challenging. Here, Ye, Toste and coworkers describe a complementary approach to these compounds using a cross-electrophile coupling (XEC) enabled by dual palladium catalysis in the presence of zirconaaziridine as an aryl shuttling platform. High cross selectivity and functional group compatibility highlight the utility of this protocol. Both DFT and experimental studies support redox transmetallation as a crucial elementary step.

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Highlights

A Zirconaaziridine-mediated Pd-catalyzed cross-electrophile coupling was developed

Negishi-type aryl-Zr coupling reactants generated *in situ* by a redox transmetallation

XEC selectivity controlled by relative rate of Pd(0) oxidative addition into aryl halide

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Zirconium-redox-shuttled cross-electrophile coupling of aromatic and heteroaromatic halides

Ting-Feng Wu,[1,4] Yue-Jiao Zhang,[1,4] Yue Fu,[3,4] Fang-Jie Liu,[1] Jian-Tao Tang,[1] Peng Liu,[3,*] F. Dean Toste,[2,5,*] and Baihua Ye[1,*]

SUMMARY

Transition metal-catalyzed cross-electrophile coupling (XEC) is a powerful tool for forging C(sp^2)–C(sp^2) bonds in biaryl molecules from abundant aromatic halides. While the synthesis of unsymmetrical biaryl compounds through multimetallic XEC is of high synthetic value, the selective XEC of two heteroaromatic halides remains elusive and challenging. Herein, we report a homogeneous XEC method, which relies on a zirconaaziridine complex as a shuttle for dual palladium-catalyzed processes. The zirconaaziridine-mediated palladium (ZAPd)-catalyzed reaction shows excellent compatibility with various functional groups and diverse heteroaromatic scaffolds. In accord with density functional theory (DFT) calculations, a redox transmetallation between the oxidative addition product and the zirconaaziridine is proposed as the crucial elementary step. Thus, cross-coupling selectivity using a single transition metal catalyst is controlled by the relative rate of oxidative addition of Pd(0) into the aromatic halide. Overall, the concept of a combined reducing and transmetallating agent offers opportunities for the development of transition metal reductive coupling catalysis.

INTRODUCTION

Heterocycles represent privileged skeletons in a wide range of pharmaceuticals, natural products, agrochemicals, and functional organic materials.[1,2] Therefore, a significant effort has been devoted toward the development of efficient methods for the synthesis of heteroaromatic arenes.[3–17] These efforts gave rise to a number of transition metal-catalyzed cross-coupling reactions, including those that led to the 2010 Nobel Prize in Chemistry.[18] In general, cross-coupling reactions produce a carbon-carbon bond through the coupling of an organometallic fragment and an (heteroaryl) aryl halide or pseudohalide (Scheme 1A).[19–23] A key elementary step in this process involves the transfer of the group on the organometallic reagent to the transition metal catalyst, in an elementary process known as transmetallation.[24] The breadth of organometallic reagents, including those derived from boron-, magnesium-, tin-, lithium-, and zinc-carbon bonds, that undergo transmetallation has enabled the development of a diverse set of transition metal-catalyzed cross-coupling reactions.[25–29] However, prior to the catalytic cross-coupling, these methods require preparation of the requisite transmetallating reagents, often from a more readily available (hetero) arylhalide through a formal reduction of the carbon-halogen bond.[21] Attempts to render both the preparation of the organometallic reagent and the catalytic coupling reaction in a single operation have proven challenging and have generally resulted in protocols that require sequential metalation (borylation) and cross-coupling via two steps in one pot.[30–32]

The bigger picture

Heteroaromatic compounds are privileged scaffolds in biologically relevant organic molecules and functional materials. While Negishi and Suzuki-Miyaura couplings are among the most powerful synthetic tools for assembling these structures, challenging and underdeveloped transition metal-catalyzed cross-electrophile coupling (XEC) of heteroaryl halides without prior formation of organometallic reagents offers a synthetically valuable entry into these molecules. Herein, we disclose a protocol involving homogeneous Pd-catalyzed zirconaaziridine redox-shuttled ZAPd-XEC of two heteroaromatic bromide and iodide compounds. This platform tolerates diverse functional groups, provides excellent cross-selectivities, and is controlled by a single Pd catalyst. The proposed redox transmetallation in the ZAPd-XEC sets the stage for the development of additional unprecedented transition metal-catalyzed processes.

Recently, multi-transition metal-catalyzed cross-electrophile coupling (XEC),[33–38] single-electron transfer cross-couplings,[39–41] and carbon-hydrogen functionalization reactions[12] have emerged as attractive alternative approaches. In order to achieve selectivity between the two (pseudo) halide precursors and to avoid homocoupling, XEC approaches rely on the differences in relative rates for production of the organometallic reagent from the organic halide in an elementary step known as oxidative addition (formal reduction of the [hetero] arylhalide). Most commonly, two transition metal catalysts, Ni and Pd, are employed, with the former undergoing rapid oxidative addition and stoichiometric reduction (for example, zinc) to generate the required organometallic reagent prior to the palladium-catalyzed cross-coupling event (Scheme 1B).[33] Despite significant progress in this field, accessing heterocyclic compounds via direct XEC of two heteroaromatic (pseudo) halides remains a formidable challenge. In order to overcome this limitation, several issues must be addressed, including the incompatibility of the heteroaromatic compounds with the organometallic coupling reagents and stoichiometric reducing agents, while maintaining selectivity for cross-coupling.[16,31]

Nevertheless, encouraged by the great value of heteroaromatic compounds, we sought an alternative platform for catalysis of both homo-electrophile coupling and XEC of readily available aromatic and heteroaromatic halides. In previously reported systems, selective *in situ* formation of one organometallic reagent under reductive coupling conditions requires that two electrophilic coupling partners have significantly different reactivities. This has generally been addressed by employing two different transition metal catalysts.[42,43] Moreover, transmetallation is pivotal to the success of these XEC reactions: first, by reducing the initially produced organo-transition metal species to the organometallic cross-coupling partner, and second, by transferring the ligand of the resulting organometallic complex to catalytically active transition metal for the cross-coupling event.[34,37] For example, in the elegant Ni/Pd-catalyzed system developed by Weix, ligand exchange between two catalytically active transition metal species involves a zinc reduction of an arylnickel species, followed by transmetallation of the arylzinc intermediate to palladium (Scheme 1B).[33,38] Similarly, Kishi et al. demonstrated that zirconocene and the stoichiometric reducing agent (Mn) allowed for Ni-catalyzed homocoupling of aromatic halides (Scheme 1C).[44] They proposed that this reaction proceeded through a mechanism involving transmetallation from arylnickel(II) to form an arylzirconium species and nickel(II) halides that were subsequently reduced by the stoichiometric metal to regenerate the active nickel(0) catalyst.

We were inspired by reports of redox-transmetallation[45] from homogeneous organometallic complexes to consider the use of a homogeneous organometallic complex as a soluble reducing agent that would also mediate rapid transmetallation from a kinetically formed (hetero) aryl-palladium(II) complex (Scheme 1D). Moreover, we envisioned that increasing the relative rate of the initial transmetallation/reduction event might preserve the selectivity imparted by the oxidative addition and allow for the use of a single transition metal catalyst in XEC. In this context, redox transmetallation of the (hetero) aromatic component is expected to be highly selective and to proceed faster than the subsequent conventional transmetallation and provide opportunities for the formation of the cross-coupled heteroaromatic-heteroaromatic products, rather than competing homocoupling adducts. We posited that zirconaaziridines (η^2-imine zirconocene), first reported by Buchwald,[46,47] would serve as potential candidates capable of undergoing redox transmetallation, thus shuttling the heteroaryl group from Pd to Zr to form a (hetero) arylzirconocene complex that could participate in traditional transmetallation and cross-coupling. This strategy, which circumvents the use of reducing

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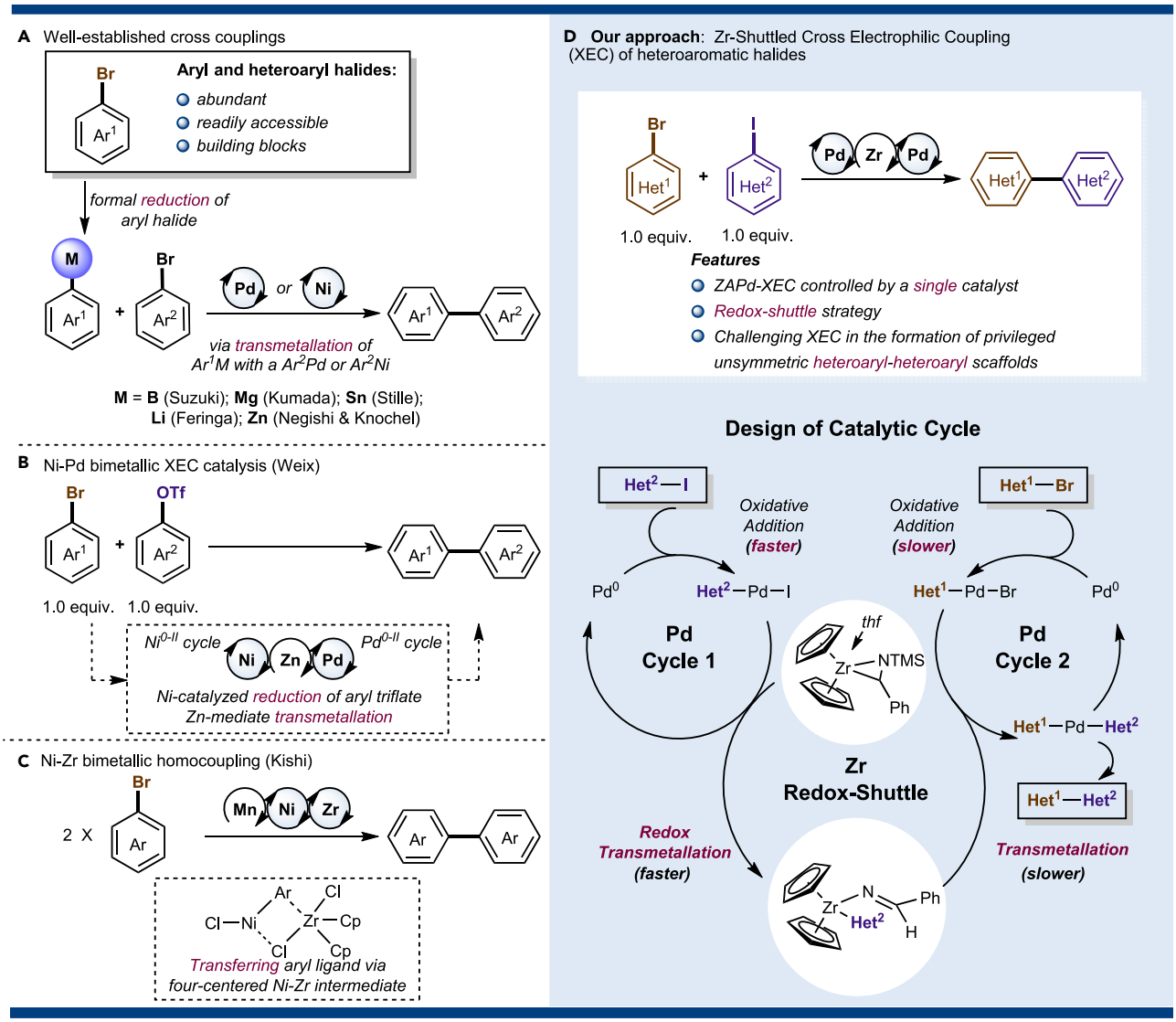


Scheme 1. Strategy for zirconaaziridine-mediated palladium (ZAPd)-catalyzed homo- and cross-electrophile coupling reactions

(A) Well-established cross-couplings.

(B) Ni-Pd bimetallic XEC catalysis reported by Weix.

(C) Ni-Zr bimetallic homocoupling reported by Kishi.

(D) Our approach of ZAPd-XEC catalysis.

agents that might be incompatible with heteroaromatic compounds, would allow for high levels of XEC selectivity by modulating the relative rate of oxidative addition of palladium(0).[48,49] On the basis of these hypotheses, we initiated our investigations of the combined zirconaaziridine/palladium (ZAPd) catalysis system in XEC reactions.

RESULTS AND DISCUSSION

ZAPd-homocoupling reaction

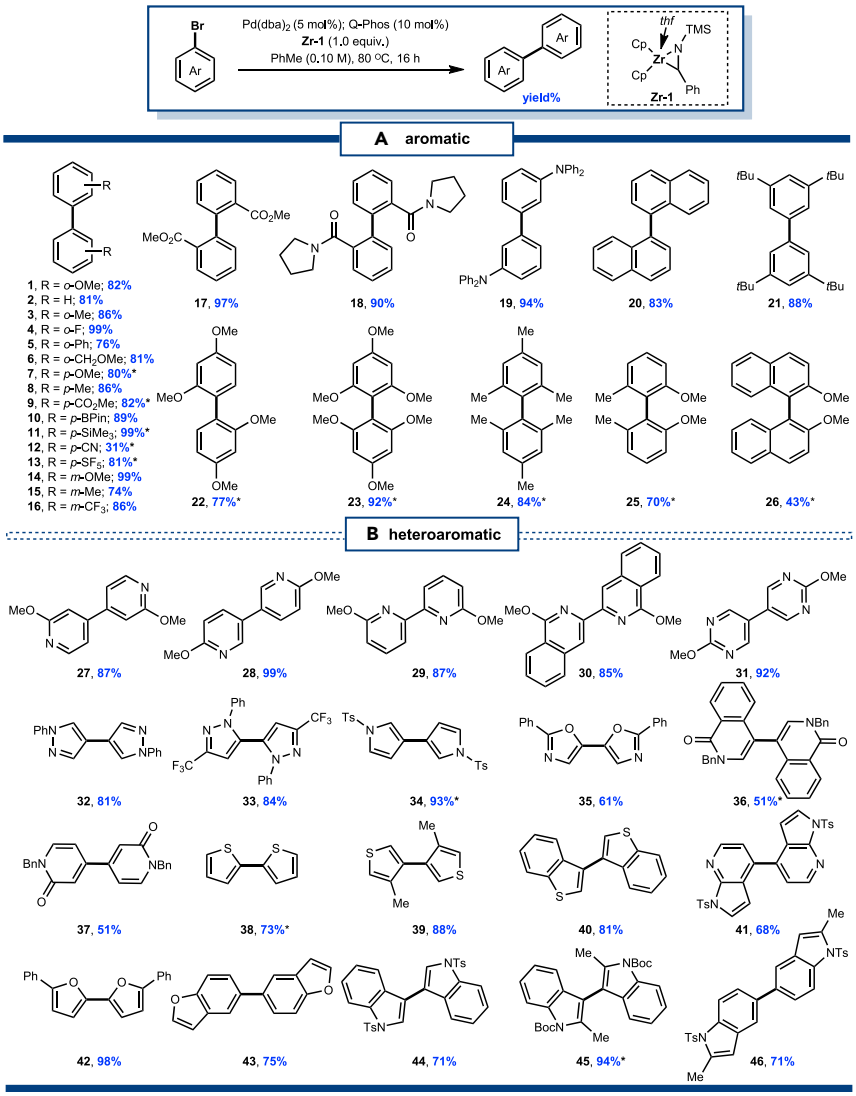
At the outset of the investigation, various reaction parameters were established for the simple homocoupling reaction of 2-bromoanisole mediated by **Zr-1**, prepared on gram scale from the commercially available Schwartz reagent,[46] and catalyzed by a phosphine-ligated palladium complex (see supplemental information, Tables

S1–S6). $P(tBu)_3$ and Q-Phos were identified as the best ligands for the formation of biaryl **1** while minimizing the formation of the simple arylhalide reduction product (Table S1). While aryl triflates were unreactive and aryl chlorides showed only a modest productive reaction, both aryl bromides and iodides underwent smooth palladium-catalyzed homocoupling, setting the stage for further investigation of this catalyst system in reductive XEC (Table S2). Notably, zirconaaziridine was required for successful homocoupling, while the precursor zirconocene dichloride gave only a low conversion of the starting aryl bromide (Table S3). These initial studies also identified 80°C–100°C as the optimal reaction temperature and toluene as the optimal solvent (Table S4 and S6).

With optimized reaction conditions for both homo-electrophile coupling and XEC in hand, we probed the generality of the ZAPd-homocoupling protocol. Various substituted aromatic bromides were first examined in the electrophile homocoupling reactions. As depicted in Scheme 2A, substituted symmetrical biaryl derivatives **3–22** bearing alkyl, aryl, silyl, fluoro, trifluoromethyl, pentafluorosulfanyl, carboalkoxy, carboxamide, and amino groups were obtained in good to excellent yields (up to 99%). Notably, biaryl products **10** and **12** bearing synthetically useful boronate and cyano groups, respectively, were accessible, despite the potential reactivity zirconaaziridines with these functional groups.[46] The construction of hindered $C(sp^2)$–$C(sp^2)$ bonds required the use of $P(tBu)_3$ as the ligand, which enabled the synthesis of 2,2′,6,6′-tetrasubstituted biaryl compounds **23–26** in good to excellent yields. These results demonstrate the simplicity and excellent functional group compatibility of the ZAPd catalyst system, and the potential of this protocol to complement traditional approaches to biaryl compounds, such as oxidative coupling[8] and the Negishi cross-coupling reaction.[23,50] Next, we turned our attention to the scope of homo-electrophile coupling of heteroaromatic bromides that have proven challenging using these traditional methods (Scheme 2B). Nitrogen-coordinating electron-deficient pyridine, isoquinoline, and pyrimidine underwent homocoupling to furnish **27–31** in excellent yields and without observation of pronounced catalyst deactivation. Homocoupling reactions of electronically different five-membered heteroaromatic bromides, including those based on oxazole, pyrazole, and pyrrole, were also feasible, affording **32–35**. Moreover, the ZAPd-homocoupling reaction of the electron-deficient isoquinolinone, and 4,4′-dipyridone heterocycles showed slightly decreased yields in the formation of **36** and **37**. On the other hand, biologically relevant heteroaromatic bromides, such as those based on thiophene, benzothiophene, furan, benzofuran, indoles, and 7-azaindole, all underwent smooth coupling to afford **38–46** with similar reactivities. The breadth of these successful homocoupling of heteroaromatic halides encouraged us to investigate the ZAPd catalyst platform to the challenging XEC of aromatics and heteroaromatics.

ZAPd-cross-electrophile coupling (XEC) reaction

Using the catalyst system described earlier, an equimolar (1: 1) ratio of aryl bromide and iodide effectively underwent ZAPd-XEC with high selectivity (80%) in favor of the cross-coupled product **47**. In contrast, a mixture of cross- and homocoupled products was observed when aromatic compounds with the same carbon-halogen bond were employed (Table S7). A re-examination of the reaction parameters showed that the effects of solvent, temperature, zirconaaziridine, and ligand on the outcome of the ZAPd-XEC reaction were similar to those found in the homocoupling reaction, with $P(tBu)_3$ providing slightly improved yields and selectivity compared with Q-Phos (Tables S8–S13). With these studies, we established $Pd(PtBu_3)_2$ (5.0 mol %) and additional $P(tBu)_3$ (10.0 mol %) with two equivalents of **Zr-1** as the conditions of choice. Conducting the ZAPd-XEC of 2-bromoanisole and iodobenzene with these parameters afforded the XEC adduct **47** in a yield of 64% and cross-coupling selectivity of 81% (Scheme 3).



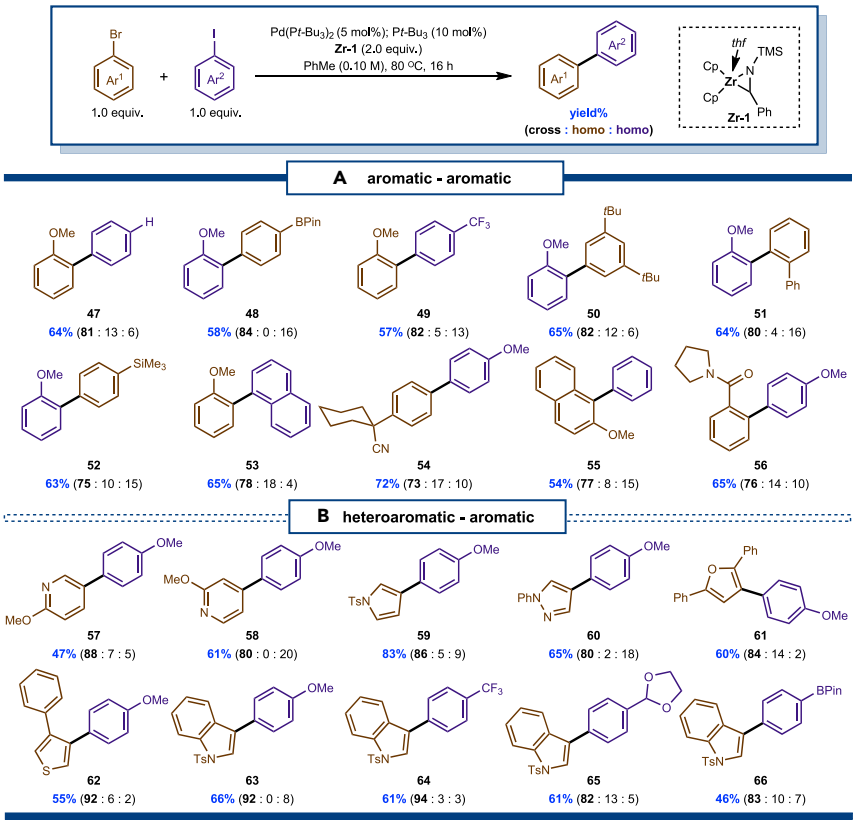
Scheme 2. Scope of ZAPd homocoupling of aryl and heteroaryl halides

Reaction conditions: Ar-Br (0.20 mmol), **Zr-1** (0.20 mmol), $Pd(dba)_2$ (10 μmol, 5.0 mol %), Q-Phos (20 μmol, 10.0 mol %), PhMe (2.0 mL, 0.10 M), 80°C, 16 h. *$PtBu_3$ was used instead of Q-Phos.

(A) Homocoupling of aromatic halides.

(B) Homocoupling of heteroaromatic halides.

Using these conditions, a wide range of unsymmetrical biaryl compounds (**47–56**), including those bearing boronic ester, trifluoromethyl, trimethylsilyl, and carboxamide groups, underwent the desired ZAPd-XEC reaction with cross-coupling selectivities of approximately 80% in most cases (Scheme 3A). Interestingly, compound **54** bearing a cyano group was isolated in a yield of 72%, despite with slightly lower selectivity (73%). The ZAPd-XEC of 4-iodoanisole to various heteroaromatic coupling partners was examined next (Scheme 3B). Cross-coupling with 6-methoxy pyridyl derivatives led to the formation of **57** and **58** with selectivities of 88% and 80%, respectively. Similar results were obtained when the pyridyl fragment was replaced with bromides derived from other heteroaromatic compounds frequently represented in pharmaceuticals (**59–63**). Notably, these examples retain excellent selectivity in favor of the heteroaromatic-aromatic cross-coupling products (up to 92% selectivity). In addition, employing aryl iodides bearing trifluoromethyl (**64**),



Scheme 3. Scope of ZAPd-XEC of aryl and heteroaryl halides

Reaction conditions: Ar^1-Br (0.10 mmol), Ar^2-I (0.10 mmol), **Zr-1** (0.20 mmol), Pd(Pt-Bu_3)$_2$ (5.0 μmol, 5.0 mol %), Pt-Bu_3 (10 μmol, 10.0 mol %), PhMe (1.0 mL, 0.10 M), 80°C, 16 h.

(A) Cross electrophilic coupling of aromatic halides.

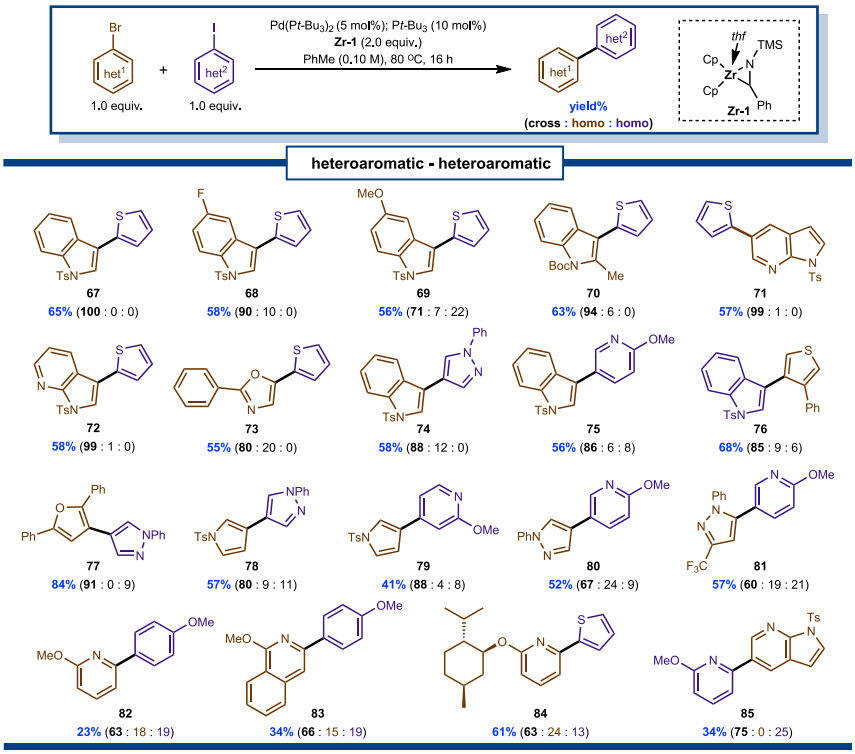
(B) Cross electrophilic coupling of heteroaromatic and aromatic halides.

acetal (**65**), and boronate (**66**) substituents in the ZAPd-XEC reaction further demonstrates the potential synthetic value of this catalyst system.

Encouraged by the aforementioned successful results, the unprecedented XEC between heteroaryl bromides and iodides was examined (Scheme 4). ZAPd-XEC with a 1:1 ratio of 2-iodothiophene and 3-bromoindole derivatives (**67**–**69**) revealed that the cross-coupling selectivity was influenced by the nature of indole substituents. More specifically, electronically neutral or electron-deficient variants gave excellent cross-coupling selectivities (up to 100%). Pleasingly, other indole and azaindole derivatives (**70**–**72**) were also amenable to the ZAPd-XEC reaction. Cross-coupling reactions were utilized to produce various combinations of heterocycles, including oxazole-thiophene **73**, indole-pyrazole **74**, indole-pyridine **75**, indole-thiophene **76**, furan-pyrazole **77**, pyrrole-pyrazole **78**, and pyrrole-pyridine **79**, highlighting the breadth of the strategy. In addition, pyrazole **80** and pyridine **81** derivatives were also prepared using this method, although lower selectivities were observed. Finally, ZAPd-XEC reaction of substrates containing the challenging 2-pyridyl electrophilic fragment also successfully afforded the corresponding XEC products **82**–**85**, albeit in diminished yields and moderate cross-coupling selectivities.

Proposed mechanism

The proposed mechanism for ZAPd-XEC is outlined in Scheme 1D. At the outset, we considered whether the initial selectivity-determining oxidative addition might be

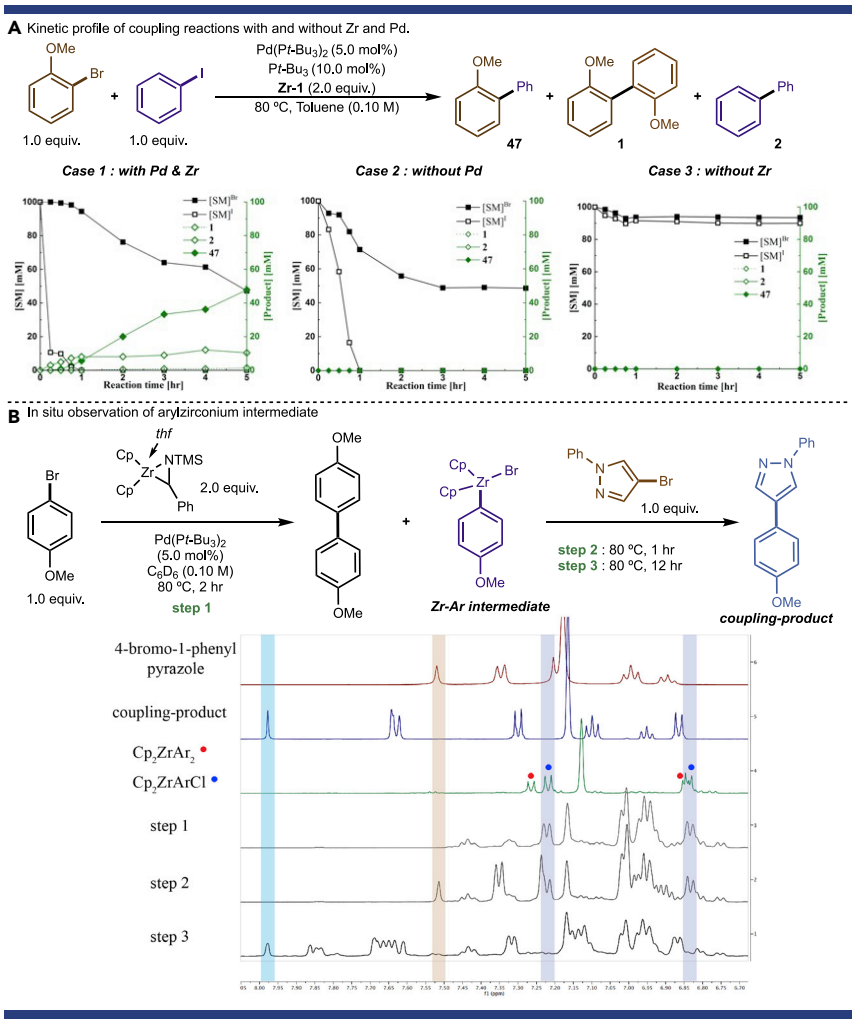


Scheme 4. Scope of ZAPd-XEC of two heteroaromatic halides

Reaction conditions: Ar^1-Br (0.10 mmol), Ar^2-I (0.10 mmol), **Zr-1** (0.20 mmol), Pd(Pt-Bu_3)$_2$ (5.0 μmol, 5.0 mol %), Pt-Bu_3 (10 μmol, 10.0 mol %), PhMe (1.0 mL, 0.10 M), 80°C, 16 h.

performed by the stoichiometric zirconaaziridine complex. While the zirconium-mediated oxidative addition to arylhalides showed chemoselectivity consistent with that required for XEC (Scheme S1; Table S14), examination of the reaction of 4-iodo-*N*-phenylpyrazole with zirconaaziridine at 60°C showed a dramatic acceleration in the conversion of the heteroarylhalide in the presence of catalytic amounts of bis(tri-*t*-butylphosphine)palladium(0) (see supplemental information, Scheme S2). Moreover, monitoring the reaction showed that zirconium-mediated consumption of the aryl iodide was rapid, but the product formation in the zirconium-mediated reaction was significantly slower than when the reaction was conducted under ZAPd-XEC conditions (Scheme 5A). More specifically, the zirconium-mediated palladium-catalyzed process showed rapid consumption (<1 h) of aryliodide with only small amounts of homocoupled product **2** formed within this time period (*Case 1*, see also Scheme S3). The conversion of the arylbromide occurred after the aryliodide was consumed and was accompanied by the generation of the heterocoupled product **47**. In contrast, the reaction with zirconaaziridine, in the absence of the palladium catalyst, showed slower consumption of the aryl iodide, followed by slower reaction with the aryl bromide, without significant formation of any coupled products (*Case 2*, see also Scheme S4). Little conversion and no product formation occurred in the absence of zirconaaziridine (*Case 3*, see also Scheme S5).

Taken together, these results are most consistent with a mechanism of palladium-mediated oxidative addition to the aryliodide leading to an arylpalladium(II) intermediate that undergoes conversion to an arylzirconium species. Importantly, these arylzirconium intermediates do not undergo exchange reactions with arylhalides (Table S15), suggesting that the initially generated arylzirconium reflects the kinetic selectivity of the palladium-catalyzed oxidative addition. Moreover, methanolysis of the reaction



Scheme 5. Mechanistic studies

(A) Kinetic profile of coupling reactions with and without zirconaaziridine complex and palladium catalyst.

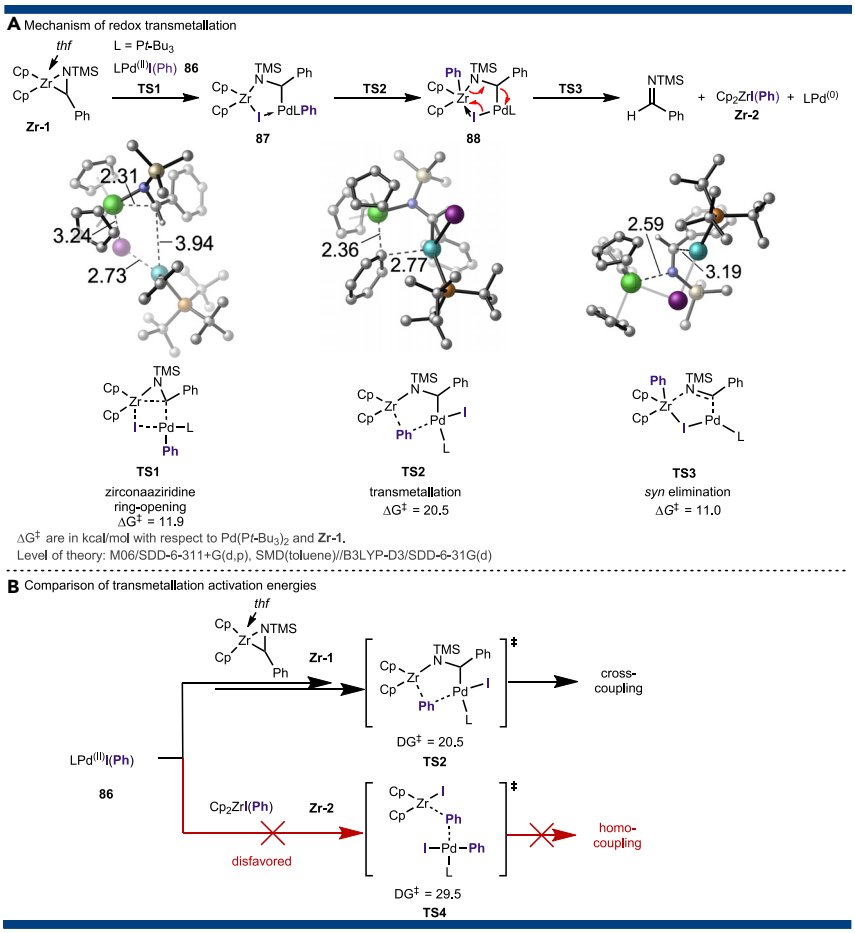
(B) *In situ* observation of aryl zirconium intermediate by ^{1}H-NMR spectroscopy.

mixture with CD_3OD afforded 1-phenyl-1*H*-pyrazole in a 49% yield with 80% deuterium incorporation at C4-position, consistent with the intermediacy of a Negishi-type heteroarylzirconium reagent[51,52] that underwent protonolysis (Equations S22–S24). On the basis of these experiments, we sought to obtain evidence for the postulated arylzirconium intermediate. To this end, the reaction of *para*-bromoanisole with zirconaaziridine, in the presence of catalytic amount of bis(tri-*t*-butylphosphine)palladium(0), was monitored by ^{1}H-NMR (Scheme 5B; see also Schemes S9 and S10). These conditions resulted in the formation of the postulated arylzirconium intermediate, as confirmed by comparison with an authentic sample. The addition of bromopyrazole to the reaction mixture produced the desired coupling product, consistent with the viability of the arylzirconium intermediate in downstream Negishi-type coupling events. Similar experiments were performed with the homocoupling pathway for the formation of 4,4′-dimethoxybiphenyl **7** (see supplemental information). Importantly, these observations suggest that the redox transmetallation proceeds faster than the subsequent conventional transmetallation, thereby allowing for the observed XEC selectivity.

Having established that the initial oxidative addition is palladium mediated, we sought to explore the mechanism of the transmetallation event between the arylpalladium(II) halide intermediate and zirconaaziridine. In addition to furnishing an arylzirconium(IV) species for further Negishi-type cross-coupling,[53] the reaction of the zirconaaziridine with the arylpalladium(II) halide must regenerate palladium(0), in the absence of exogenous reductant, for the subsequent oxidative addition. Experiments with deuterium-labeled η^2-imine zirconocene (Schemes S7 and S8) complexes suggest that redox chemistry leveraging the imine C–H bond, including those involving beta-hydrogen elimination, are not operative. Instead, drawing on the studies of Norton,[54] we favor a process in which a coordinately unsaturated Lewis-acidic palladium(II) complex reacts with the zirconaaziridine through a formal sigma-bond metathesis.[55] The bimetallic intermediate can then generate the requisite palladium(0) catalyst, the arylzirconocene intermediate, and the imine, without the scrabbling of the imine C–H bond (see supplemental information, figures in Schemes S7 and S8).

This proposed transmetallation mechanism is supported by computational studies through DFT calculations (see supplemental information for computational details and results for less favorable pathways). In the "Pd Cycle 1" (Scheme 1D), oxidative addition of PhI to palladium(0) (**TS5**, $\Delta G^{\ddagger}$ = 16.5 kcal/mol) forms phenylpalladium(II) iodide (**86**). We computed several possible transmetallation pathways of **86** with **Zr-1** (Scheme S12). The lowest-energy pathway (Scheme 6A) follows a facial zirconaaziridine ring opening via σ-bond metathesis with the Pd–I bond of **86** (**TS1**, $\Delta G^{\ddagger}$ = 11.9 kcal/mol) to cleave the Zr–C bond in **Zr-1** and generate a bimetallic intermediate **87**. Alternative mechanisms for zirconaaziridine ring opening, including backside (**TS6**, $\Delta G^{\ddagger}$ = 34.1 kcal/mol)- and frontside(**TS7**, $\Delta G^{\ddagger}$ = 31.3 kcal/mol)-bimolecular electrophilic substitutions, and σ-bond metathesis with the Pd–Ph bond of **86** (**TS8**, $\Delta E^{\ddagger}$ = 27.1 kcal/mol) require higher activation barriers. In addition, a σ-bond metathesis process involving the Zr–N bond of **Zr-1** is even less favorable (**TS9**, $\Delta G^{\ddagger}$ = 52.4 kcal/mol). The higher activation energy for the Zr–N bond cleavage is consistent with the observation that the imine C–H(D) bonds were not scrambled (Scheme S8) because the C–H(D) scrambling would require a β-hydrogen elimination from the Zr–N bond cleavage intermediate. After the zirconaaziridine ring opening, transmetallation of the phenyl group to zirconium occurs in two separate steps: intramolecular phenyl group transfer proceeds through **TS2** ($\Delta G^{\ddagger}$ = 20.5 kcal/mol), followed by a facial and irreversible *syn* E2-type elimination (**TS3**, $\Delta G^{\ddagger}$ = 11.0 kcal/mol) to produce phenylzirconocene (**Zr-2**) and regenerate the Pd(0) catalyst. Overall, the redox transmetallation from **Zr-1** to **Zr-2** is exergonic by 16.0 kcal/mol. The exothermicity of the redox transmetallation agrees with the aforementioned *in situ* detection of arylzirconium species (Scheme 5B). To form the final XEC product, **Zr-2** undergoes transmetallation with LPdBr(Ph) formed in the "Pd Cycle 2" with an activation free energy of 34.5 kcal/mol (see **supplemental information** for full details).

Finally, to gain an additional insight into the origin of the selectivity of the ZAPd-XEC coupling, we calculated the homocoupling pathway via transmetallation between phenylpalladium(II) iodide (**86**) and phenylzirconium **Zr-2** (Scheme 6B). The barrier to this traditional transmetallation (**TS4**, $\Delta G^{\ddagger}$ = 29.5 kcal/mol) is 9.0 kcal/mol higher than that for the redox transmetallation. This reactivity difference provides the likely reason as to why XEC can be achieved—arylpalladium(II) species are more likely to engage in reaction with the zirconaaziridine than in traditional Negishi coupling with the *in situ*-formed arylzirconium species. Therefore, the homocoupling pathway is suppressed due to the lower barrier for redox transmetallation.



Scheme 6. Computational studies

(A) Mechanism of redox transmetallation.

(B) Comparison of transmetallation activation energies.

Conclusions

In summary, we have elaborated a general and robust protocol for both catalytic homo-electrophile coupling and XEC of aromatic and heteroaromatic halides. It is noteworthy that the ZAPd-XEC methodology offers an entry into biologically relevant unsymmetrical heterocycles from the pool of available heteroaromatic halides. Excellent cross-selectivities together with tolerance of a wide range of functional groups highlight the potential of ZAPd-XEC. In particular, redox transmetallation of zirconaaziridine with Ar-Pd^{II}-I, thus accumulating one Ar-Zr species for subsequent transmetallation, plays a crucial role in the control of XEC selectivity. More broadly, this process may provide new opportunities to explore redox-shuttling using zirconaaziridine in other reductive transition metal-catalyzed processes.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, F. Dean Toste (fdtoste@berkeley.edu).”

Materials availability

Full experimental details as well as detailed computational studies of reaction mechanisms can be found in the supplemental information.

Data and code availability

All data supporting this study are available in the manuscript and supplemental information.

Full experimental procedures are provided in the supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2021.06.007.

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AUTHOR CONTRIBUTIONS

B.Y. and F.D.T. conceived and directed the project. T.W. and Y.Z. carried out the experiments with B.Y. providing guidance. F.-J.L. and J.-T.T. carried out the preparation of starting materials. Y.F. and P.L. studied the mechanisms using DFT calculations. B.Y., P.L., and F.D.T. wrote the manuscript with the input of all other authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES

1. Boldi, A.M. (2004). Libraries from natural product-like scaffolds. Curr. Opin. Chem. Biol. *8*, 281–286.
2. Ackermann, L. (2009). Modern Arylation Methods (Wiley).
3. Hassan, J., Sévignon, M., Gozzi, C., Schulz, E., and Lemaire, M. (2002). Aryl-aryl bond formation one century after the discovery of the Ullmann reaction. Chem. Rev. *102*, 1359–1470.
4. Cacchi, S., and Fabrizi, G. (2005). Synthesis and functionalization of indoles through palladium-catalyzed reactions. Chem. Rev. *105*, 2873–2920.
5. Campeau, L.C., and Fagnou, K. (2007). Applications of and alternatives to pi-electron-deficient azine organometallics in metal catalyzed cross-coupling reactions. Chem. Soc. Rev. *36*, 1058–1068.
6. Alberico, D., Scott, M.E., and Lautens, M. (2007). Aryl−aryl bond formation by transition-metal-catalyzed direct arylation. Chem. Rev. *107*, 174–238.
7. Hapke, M., Brandt, L., and Lützen, A. (2008). Versatile tools in the construction of substituted 2,2′-bipyridines-cross-coupling reactions with tin, zinc and boron compounds. Chem. Soc. Rev. *37*, 2782–2797.
8. Liu, C., Zhang, H., Shi, W., and Lei, A. (2011). Bond formations between two nucleophiles: transition metal catalyzed oxidative cross-coupling reactions. Chem. Rev. *111*, 1780–1824.
9. Yeung, C.S., and Dong, V.M. (2011). Catalytic dehydrogenative cross-coupling: forming carbon-carbon bonds by oxidizing two carbon-hydrogen bonds. Chem. Rev. *111*, 1215–1292.
10. Bringmann, G., Gulder, T., Gulder, T.A.M., and Breuning, M. (2011). Atroposelective total synthesis of axially chiral biaryl natural products. Chem. Rev. *111*, 563–639.
11. Sun, C.L., and Shi, Z.J. (2014). Transition-metal-free coupling reactions. Chem. Rev. *114*, 9219–9280.
12. Yang, Y., Lan, J., and You, J. (2017). Oxidative C–H/C–H coupling reactions between two (hetero)arenes. Chem. Rev. *117*, 8787–8863.
13. Zweig, J.E., Kim, D.E., and Newhouse, T.R. (2017). Methods utilizing first-row transition

metals in natural product total synthesis. Chem. Rev. *117*, 11680–11752.

14. Gandeepan, P., Müller, T., Zell, D., Cera, G., Warratz, S., and Ackermann, L. (2019). 3d transition metals for C−H activation. Chem. Rev. *119*, 2192–2452.

15. Cook, X.A.F., de Gombert, A., McKnight, J., Pantaine, L.R.E., and Willis, M.C. (2021). The 2-pyridyl problem: challenging nucleophiles in cross-coupling arylations. Angew. Chem. Int. Ed. Engl. *60*, 11068–11091.

16. Zhou, M., Tsien, J., and Qin, T. (2020). Sulfur(IV)-mediated unsymmetrical heterocycle cross-couplings. Angew. Chem. Int. Ed. Engl. *59*, 7372–7376.

17. Liu, K., Li, N., Ning, Y., Zhu, C., and Xie, J. (2019). Gold-catalyzed oxidative biaryl cross-coupling of organometallics. Chem *5*, 2718–2730.

18. Suzuki, A. (2011). Cross-coupling reactions of organoboranes: an easy way to construct C–C bonds (Nobel Lecture). Angew. Chem. Int. Ed. *50*, 6722–6737.

19. King, A.O., and Yasuda, N. (2004). Palladium-catalyzed cross-coupling reactions in the synthesis of pharmaceuticals. Top. Organomet. Chem. *6*, 205–245.

20. Magano, J., and Dunetz, J.R. (2011). Large-scale applications of transition metal-catalyzed couplings for the synthesis of pharmaceuticals. Chem. Rev. *111*, 2177–2250.

21. Nishihara, Y. (2013). Applied Cross-Coupling Reactions (Springer).

22. Giannerini, M., Fañanás-Mastral, M., and Feringa, B.L. (2013). Direct catalytic cross-coupling of organolithium compounds. Nat. Chem. *5*, 667–672.

23. Greshock, T.J., Moore, K.P., McClain, R.T., Bellomo, A., Chung, C.K., Dreher, S.D., Kutchukian, P.S., Peng, Z., Davies, I.W., Vachal, P., et al. (2016). Synthesis of complex druglike molecules by the use of highly functionalized bench-stable organozinc reagents. Angew. Chem. Int. Ed. Engl. *55*, 13714–13718.

24. Osakada, K. (2003). Chapter 5 – transmetalation. Current Methods in Inorganic Chemistry *3*, 233–291.

25. Lennox, A.J.J., and Lloyd-Jones, G.C. (2013). Transmetalation in the Suzuki–Miyaura coupling: the fork in the trail. Angew. Chem. Int. Ed. Engl. *52*, 7362–7370.

26. Fyfe, J.W.B., Fazakerley, N.J., and Watson, A.J.B. (2017). Chemoselective Suzuki–Miyaura cross-coupling via kinetic transmetallation. Angew. Chem. Int. Ed. Engl. *56*, 1249–1253.

27. Thomas, A.A., and Denmark, S.E. (2016). Pre-transmetalation intermediates in the Suzuki-Miyaura reaction revealed: the missing link. Science *352*, 329–332.

28. de Gombert, A., McKay, A.I., Davis, C.J., Wheelhouse, K.M., and Willis, M.C. (2020). Mechanistic studies of the palladium-catalyzed desulfinative cross-coupling of aryl bromides and (hetero)aryl sulfinate Salts. J. Am. Chem. Soc. *142*, 3564–3576.

29. Jin, L., Xin, J., Huang, Z., He, J., and Lei, A. (2010). Transmetalation is the rate-limiting step: quantitative kinetic investigation of nickel-catalyzed oxidative coupling of arylzinc reagents. J. Am. Chem. Soc. *132*, 9607–9609.

30. Molander, G.A., Trice, S.L.J., Kennedy, S.M., Dreher, S.D., and Tudge, M.T. (2012). Scope of the palladium-catalyzed aryl borylation utilizing bis-boronic acid. J. Am. Chem. Soc. *134*, 11667–11673.

31. Molander, G.A., Trice, S.L.J., and Tschaen, B. (2015). A modified procedure for the palladium catalyzed borylation/Suzuki-Miyaura cross-coupling of aryl and heteroaryl halides utilizing bis-boronic acid. Tetrahedron *71*, 5758–5764.

32. Takagi, J., Takahashi, K., Ishiyama, T., and Miyaura, N. (2002). Palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron with 1-alkenyl halides or triflates: convenient synthesis of unsymmetrical 1,3-Dienes via the borylation-coupling sequence. J. Am. Chem. Soc. *124*, 8001–8006.

33. Ackerman, L.K.G., Lovell, M.M., and Weix, D.J. (2015). Multimetallic catalysed cross-coupling of aryl bromides with aryl triflates. Nature *524*, 454–457.

34. Everson, D.A., and Weix, D.J. (2014). Cross-electrophile coupling: principles of reactivity and selectivity. J. Org. Chem. *79*, 4793–4798.

35. Goldfogel, M.J., Huang, L., and Weix, D.J. (2020). Chapter 9 cross-electrophile coupling. Nickel Catalysis in Organic Synthesis: Methods and Reactions S. Ogoshi (Wiley-VCH Verlag). https://doi.org/10.1002/9783527813827.ch9.

36. Olivares, A.M., and Weix, D.J. (2018). Multimetallic Ni- and Pd-catalyzed cross-electrophile coupling to form highly substituted 1,3-dienes. J. Am. Chem. Soc. *140*, 2446–2449.

37. Biswas, S., and Weix, D.J. (2013). Mechanism and selectivity in nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides. J. Am. Chem. Soc. *135*, 16192–16197.

38. Kang, K., Huang, L., and Weix, D.J. (2020). Sulfonate versus sulfonate: nickel and palladium multimetallic cross-electrophile coupling of aryl triflates with aryl tosylates. J. Am. Chem. Soc. *142*, 10634–10640.

39. Poremba, K.E., Kadunce, N.T., Suzuki, N., Cherney, A.H., and Reisman, S.E. (2017). Nickel-catalyzed asymmetric reductive cross-coupling to access 1,1-diarylalkanes. J. Am. Chem. Soc. *139*, 5684–5687.

40. Knappke, C.E., Grupe, S., Gärtner, D., Corpet, M., Gosmini, C., and Jacobi von Wangelin, A. (2014). Reductive cross-coupling reactions between two electrophiles. Chemistry *20*, 6828–6842.

41. Durandetti, M., Nédélec, J.Y., and Périchon, J. (1996). Nickel-catalyzed direct electrochemical cross-coupling between aryl halides and activated alkyl halides. J. Org. Chem. *61*, 1748–1755.

42. Krasovskiy, A., Duplais, C., and Lipshutz, B.H. (2009). Zn-mediated, Pd-catalyzed cross-couplings in water at room temperature without prior formation of organozinc reagents. J. Am. Chem. Soc. *131*, 15592–15593.

43. Czaplik, W.M., Mayer, M., and Jacobi von Wangelin, A.J. (2009). Domino iron catalysis: direct aryl–alkyl cross-coupling. Angew. Chem. Int. Ed. Engl. *48*, 607–610.

44. Peng, J., Liu, X., and Kishi, Y. (2011). Catalytic homocoupling of aryl, alkenyl, and alkynyl halides with Ni(II)-complexes and zirconocene dichloride. Tetrahedron Lett *52*, 2172–2175.

45. Marshall, J.A. (2000). Synthesis and reactions of allylic, allenic, vinylic, and arylmetal reagents from halides and esters via transient organopalladium Intermediates. Chem. Rev. *100*, 3163–3186.

46. Buchwald, S.L., Watson, B.T., Wannamaker, M.W., and Dewan, J.C. (1989). Zirconocene complexes of imines. General synthesis, structure, reactivity, and in situ generation to prepare geometrically pure allylic amines. J. Am. Chem. Soc. *111*, 4486–4494.

47. Broene, R.D., and Buchwald, S.L. (1993). Zirconocene complexes of unsaturated organic molecules: new vehicles for organic synthesis. Science *261*, 1696–1701.

48. Senn, H.M., and Ziegler, T. (2004). Oxidative addition of aryl halides to palladium(0) complexes: a density-functional study including solvation. Organometallics *23*, 2980–2988.

49. Stille, J.K., and Lau, K.S.Y. (1977). Mechanisms of oxidative addition of organic halides to group 8 transition-meta complexes. Acc. Chem. Res. *10*, 434–442.

50. Haas, D., Hammann, J.M., Greiner, R., and Knochel, P. (2016). Recent developments in Negishi cross-coupling reactions. ACS Catal *6*, 1540–1552.

51. Harris, C.F., Ravindranathan, D., and Huo, S. (2012). Oxidative addition of heteroaromatic halides to Negishi reagent and subsequent cross-coupling reactions. Tetrahedron Lett *53*, 5389–5392.

52. Marek, I. (2002). Titanium and Zirconium in Organic Synthesis (Wiley-VCH Verlag).

53. Yan, X., and Xi, C. (2017). Advances in transmetalation reactions originated from organozirconium compounds. Coord. Chem. Rev. *350*, 275–284.

54. Harlan, C.J., Bridgewater, B.M., Hascall, T., and Norton, J.R. (1999). Reaction of the Lewis acids $B(C_6F_5)_3$ and $(AlMe_2Cl)_2$ with azazirconacycles. Organometallics *18*, 3827–3834.

55. Budzelaar, P.H.M., Hughes, D.L., Bochmann, M., Macchioni, A., and Rocchigiani, L. (2020). H_2 activation by zirconaziridinium ions: σ-bond metathesis versus frustrated Lewis pair reactivity. Chem. Commun. (Camb) *56*, 2542–2545.