A monometallic approach for the C(sp^2)–C(sp^2) cross-electrophile coupling: Bypassing the demand of transmetalation

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Transition metal catalyzed cross-coupling is a versatile tool for the construction of (hetero)biaryl scaffolds. However, the cross-electrophile coupling using abundant (hetero)aryl halides and pseudohalides is still in its infancy. In particular, a robust and general method for the cross-electrophile coupling would allow unparalleled entry into the vast collection of commercially available, structurally-diverse (hetero)aryl halides and pseudohalides as coupling partners. We demonstrate herein a ligand controlled visible light driven monometallic cross-electrophile coupling platform in which the synergistic operation of dual palladium catalytic cycle differentiates the electrophiles based on the bond dissociation enthalpy. This method is mild, robust, selective, and displays unique efficacy towards a wide range of functional groups and challenging heteroaryls, providing access to structurally diverse (hetero)biaryl scaffolds. The power of the transformation has been revealed through the synthesis of (hetero)biaryl core of various pharmaceuticals, and diversification of peptides. The synthesis of more than 54% new (hetero)biaryl core has been demonstrated, allowing access to an expanded chemical space for further exploration in functional materials, drug discovery, and bioconjugation-based therapeutics development. Bypassing the traditional transmetalation step, this technology enables a general strategy for the cross-electrophile coupling of (hetero)aryl halides and pseudohalides.

The (hetero)biaryl motif is a highly privileged structural element in a vast array of biologically active molecules, agrochemicals, ligands, and functional materials[1-5]. Transition metal catalyzed traditional cross-coupling has revolutionized the landscape of molecule construction over the past several decades by forging C(sp^2)–C(sp^2) bond through the linking of a (hetero)aryl halide or pseudohalide with a (hetero)aryl nucleophile[6-8]. In general, the catalytic paradigm of these cross-coupling reactions involves a combination of three elementary steps--oxidative addition, transmetalation, and reductive elimination, offering a highly modular, although general approach to fragment coupling[9] (Fig. 1a). Despite its success and versatility, this cross-coupling method suffers from several limiting factors such as: a) poor availability and instability of (hetero)aryl nucleophile equivalents[10-12]; b) challenges in the synthesis and purification of (hetero)aryl nucleophile equivalents[6,13,14]; c) highly reactive nature of many organometallic reagents requires elaborate anaerobic conditions and impose restrictions on the use of substrates containing electrophilic functional groups or acidic protons[6]. Therefore, substantial efforts have been devoted into creating a more effective alternative synthetic protocol for building (hetero)biaryls. In this vein, direct C−H arylation[15-17] and high valent sulfur[18] and phosphorus[19] mediated cross-coupling strategies have been developed which perform remarkably well to access challenging (hetero)biaryls. These methods circumvent some of the obstacles that cross-coupling presents in terms of substrate availability and stability. Nevertheless, substrate specificity and C–H bond site-selectivity could be significant limitations of these protocols.

However, cross-electrophile coupling (XEC) approach would be a powerful tool for the construction of (hetero)biaryl moiety because of the widespread availability and stability of (hetero)aryl electrophiles[20] (Fig. 1b). Although the symmetric Ullmann coupling has been well known for more than a century, cross coupling of two unsymmetrical aryl electrophiles has not found extensive application until recently because of the competing homo-dimer formation[21,22]. Methods such as one-pot, two-step coupling[23,24] and reductive cross-coupling[25,26], in which stoichiometric metal reductant controls the sequential oxidative addition of catalytic metal complex to (hetero)aryl halides, have been developed over the years to overcome this difficulty. Notably, the later coupling approach would be effective only when two electrophilic coupling partners have significantly different reactivities. Weix[27-30], Toste and Ye[31] independently developed multimetallic catalysis strategy, which relies on the in situ generation of organometallic aryl intermediate to facilitate the transmetalation step, for the cross-electrophile coupling. Despite these advances in the field of cross-electrophile coupling, the most significant challenges persist. These include the substrate specificity, the use of multimetallic systems to distinguish reactivity, the utilization of super stoichiometric metal reductants such as Zn, Mn, Mg, etc., or the incorporation of specially synthesized zirconaaziridine complex.

We recognized that, in order to truly harness the potential of cross-electrophile coupling, it would be necessary to conceive a new catalytic paradigm that would allow direct coupling of a diverse array of (hetero)aryl electrophiles without involving multiple metal systems to differentiate the reactivity of substrates and/or facilitate the transmetalation step. Visible light mediated excited-state palladium catalysis has the ability to engender hybrid aryl Pd(I)-radical species from respective aryl (pseudo)halides *via* single electron transfer[32-35]. During this SET process, the singly occupied molecular orbital (SOMO) of the triplet-excited state [$L_nPd(0)$]* is known to be localized on Pd and stabilized by mixing with the σ* orbital of the C–X bond, leading to the rupture of C–X bond and the formation of the Pd–X bond, resulting in the formation of hybrid aryl Pd-radical species[36]. The bond dissociation energy of the C–X bond in aryl halides varies significantly from I to Cl[37]. Being the lowest bond dissociation energy of C–I bond in aryl iodide, the σ* orbital of the C–I bond are lower in energy as compared to aryl bromides and chlorides. As a consequence, the energy gap between the SOMO of the triplet-excited state [$L_nPd(0)$]* and the σ* orbital of the C–I bond (LUMO; lowest unoccupied molecular orbital) would be much less, leading to the better mixing of these two orbitals and driving the reaction more efficiently as compared to other aryl halides towards the rupture of the C–I bond and the formation of the hybrid aryl Pd-radical species. With this in mind, we hypothesized that this excited-state palladium catalysis could allow us to differentiate aryl (pseudo)halides based on their bond dissociation enthalpy (BDE). Subsequently we questioned if an open-shell Pd-photocatalytic cycle might be merged with Pd-cross-coupling cycle to render a new catalysis paradigm for cross-selective (hetero)biaryl formation by directly utilizing either two different combination of (hetero)aryl halides or a combination of (hetero)aryl halide and triflate. In this context, we envisioned that the relative rate of formation of hybrid aryl Pd(I)-radical species from aryl iodides/triflates and ancillary ligand controlled Pd(II) oxidative addition complex from aryl bromides/chlorides might be a crucial factor to harness the cross-selectivity. On this basis, we herein report the development of a palladium-based new catalytic system for the successful realization of cross-electrophile coupling of (hetero)aryl halides and pseudohalides in the presence of visible light (Fig. 1c).

The proposed mechanism for this cross-electrophile coupling is outlined in Fig 2a. Upon visible light excitation, the in situ generated $L_nPd(0)$ complex would access a triplet excited state species [$L_nPd(0)$]* (**2**). In the excited state, an open coordination site can selectively allow the association of aryl iodide/triflate **3** with Pd center, thereby furnishing a hybrid aryl Pd(I)-radical species **4** *via* an inner sphere single electron transfer (SET). In the cross-coupling cycle, the Pd(0) species, generated in-situ from a Pd(II) precatalyst is expected to undergo facile oxidative addition into an aryl bromide/chloride (**6**) to form an aryl Pd(II) species **7**. The hybrid aryl Pd(I)-radical species **4** would mediate aryl group transfer to **7**, affording the Pd(III) intermediate (**8**)[38]. Subsequently, the reductive elimination from the Pd(III) metal center would forge the requisite C–C bond, leading to the (hetero)biaryl product **9** and expelling the Pd(I) intermediate **10**. Finally, the regeneration of active Pd(0) catalyst would be achieved in presence of base[39], thereby simultaneously completing both the catalytic cycle.

With this working hypothesis in hand, we began our investigation using an equimolar ratio of 4-bromo-2-methoxypyridine (**11**) and 4-iodo-1-methyl-1*H*-pyrazole (**12**) as starting materials (Fig. 2b). We first sought to identify suitable ancillary ligand for successful realization of this synergistic monometallic catalysis approach in the presence of $Pd(OAc)_2$ as catalyst, Cs_2CO_3 as base, CH_3CN as solvent, and 456 nm blue LEDs as the visible light source. After systematic experimentation with various ligands (see supporting information for details), it was determined that only phosphine-based ligands were able to produce the desired cross-coupled product, albeit in low to moderate yields. Simple trialkylphosphines were found to have deleterious effect in this catalytic paradigm, which might be due to the lack of additional stabilizing interaction, leading to the instability of the Pd(0)

active catalyst supported by this class of ligands. The electron rich biaryl monophosphines were identified as the relatively good ligands for the formation of cross-coupled product **13** in moderate yield with reasonable selectivity (Fig. 2b). The better performance of electron rich ligand might arise from the stability of $L_nPd(0)$ active catalyst as well as improved reactivity towards oxidative addition with **11**. As ancillary ligands have been found to have a huge impact on this dual palladium based catalytic cycle, we next set out to design ligands for the further improvement in yield of **13**. The following factors were taken into consideration for designing the ligands: a) presence of non-covalent interactions which are shown to have influential effects on transition metal catalysts, b) modulation of steric and electronic properties to influence elementary steps[40]. Accordingly, we have developed a new class of bench-stable phosphine ligands, namely SudipPhos (**L79**), to access highly selective formation of desired cross-coupled product **13** in excellent yield (86%). The inclusion of NMe_2 groups at 2,4-position of the bottom ring of this biphenyl phosphine modulate its stereoelectronic properties in such a way that it can serve dual function of stabilizing the active Pd(0) complex via a π-interaction and increasing the electron density at Pd in the active catalyst resulting in facile oxidative addition (Fig. 2c). Furthermore, the NMe_2 group at 2-position maintains an optimum steric bulk along the biaryl axis of the ligand which might simultaneously decrease the energy barrier of the direct reductive elimination from transitory Pd(III) intermediate **8**. The choice of base and solvent was also crucial for successful realization of this protocol. While the use of alternative potassium containing phosphate, carbonate, acetate bases resulted in a significantly decreased yield, sodium and lithium containing bases did not produce the desired cross-coupled product (**13**) at all. However, organic bases such as DIPEA and 1,2,2,6,6-pentamethylpiperidine (PMP) were moderately effective for this transformation (Fig. 2d). Other polar and non-polar solvents, such as DMF, THF, Et_2O, hexane, and acetone resulted in poor yield of **13** (see Supplementary Table 5). Several control reactions confirmed the necessity of metal catalyst systems, base, solvent and light source (see Supplementary Table 7). To ensure that the observed cross-selectivity was the result of synergy between the two proposed catalysis mode of palladium, we performed two sets of reactions. First we examined the comparative reactivity of iodo and bromo coupling partners for a SET event in the presence of excited state palladium catalyst. An equimolar mixture of **11** and **12** was reacted with 4-*tert*-butylstyrene under standard conditions, affording only the pyrazole coupled product in 95% yield, but bromo starting material remained as such (Fig. 2e). This result validates our proposed hypothesis of reactivity differentiation based on bond dissociation enthalpy. Secondly, the reaction with stoichiometric amount of independently synthesized oxidative addition complex of **12** afforded the cross-coupled product only in 10% yield, which demonstrate that the single catalytic cycle is poorly effective (Fig. 2f). These findings are consistent with the formation of selective cross-product from our proposed mechanistic hypothesis.

With these optimal reaction conditions, we next set out to evaluate the generality of this method. Because of the challenges impeded by the heteroaryl cores, more specifically base sensitive heteroaryls such as pyrazole, thiophene, thiazole, benzothiophene, benzofuran as well as 2-pyridyls in cross-coupling, we first turned our attention to synthesize heterobiaryls (Fig. 3a). Gratifyingly, both electron-rich and electron-poor pyridyl bromides were coupled with 4-iodo-1-methyl-1*H*-pyrazole successfully, providing the corresponding biheteroaryls in good yields, irrespective of pyridyl bromide regiochemistry (**13**, **18**-**22**). The electron-rich pyridyl bromides afforded the desired products in 65-82% yields with excellent cross-selectivity. While no side products were obtained from the corresponding coupling partners in case of **13**, **18**, **19**, only protodehalogenation product from pyridyl bromide coupling partner was obtained in 10% yield in case of **20**. The electron-deficient pyridyl halide afforded the desired cross-coupled product **21** in poor yield (20%) with our optimized reaction conditions. Re-examination of the other bases led to a new set of conditions utilizing PMP instead of Cs_2CO_3 that completely suppressed the side reactions (i.e. homocoupling and protodehalogenation from both the partners) and delivered the products **21**, **22** in 70% and 78% yields, respectively (see Supplementary Table 9). Sterically demanding pyrazole substrate with 3,5-disubstitution could also be coupled with pyridyl bromide in 62% yield (**23**). Interestingly, neither homocoupling nor protodehalogenation products were observed in this case. This method was effective for the synthesis of various bipyridyl and pyridylpyrimidine cores (**24**-**27**), which are the key structural elements of antibiotics such as caerulomycins and collismycins, fungicides as well as tyrosine kinase inhibitors[41]. The synthesis of bipyridyls where both the pyridyl cores are electron-deficient remain a challenging task in cross-coupling because of the instability, and expensiveness of the electron-deficient boronic acids, which not only requires an extra step but also demands special care to their synthesis from the much cheaper, stable, and easily available halide analogues. This protocol was quite effective in synthesizing challenging electron-deficient bipyridyls **24**, **25** in 65% and 60% yields by directly utilizing the respective pyridyl halides. The substrate containing the challenging 2-pyridyl electrophilic fragment successfully provided the corresponding cross-coupled products **26**, **27** in 63% and 72% yields, respectively with exclusive selectivity. Notably, the natural product (±)-cytisine, a partial agonist at neuronal nicotinic receptors can be synthesized in three step from **26**, which was previously synthesized *via* insitu Stille or Suzuki coupling in poor yield (40%)[42]. While the synthesis of biheterocycles comprising of 6-/5-membered heteroaryls and 6-/6-membered heteroaryls proved to be viable, we found that the coupling between much more electronically richer 5-membered heteroaryl halides led to low yields due to consumption of only a minimal amount of substrate. Relative to six-membered heteroaryls, five-membered heteroaryls are considered to be a difficult class of substrates in the domain of Pd-catalyzed cross-coupling mainly because of the three reasons -- a) instability of their boronic acid derivatives, b) ability to coordinate strongly with Pd, promoting catalyst deactivation with the displacement of the supporting phosphine ligand, c) presence of acidic C–H bond leading to the decomposition of sensitive five-membered cores and often suffer from regioselectivity issue in basic medium[43]. Interestingly, re-evaluation of other ligands revealed that PhSudipPhos (**L80**) was an effective ligand for the coupling of pyrazole with thiophene and thiazole, providing the corresponding cross-coupled products in 50-87% yields (**28**-**31**) with excellent cross-selectivity (see Supplementary Table 10). It is important to mention that the free (NH)-heteroarene was well tolerated in this method without competing C-N coupling and other side reactions (**31**). Coupling of fused heteroaryls with heteroaryls was also achieved using this protocol to produce various combination of biheterocycles in 52-78% yields (**32**-**38**; Fig. 3a). We next examined the scope of this protocol for the coupling of heteroaryl halides with aryl halides (Fig. 3b). Both electron-rich and electron-poor aryl halides were coupled successfully with pyrazolyl, pyrimidyl, and substituted pyridyl halides (**39**-**42**, **44, 46, 47**, **51**-**53**). The coupling of pyrimidyl bromides with electron-deficient aryl iodides led to very poor yield of the corresponding products. Re-examination of reaction conditions revealed that a combination of organic base (PMP) and PhSudipPhos ligand was able to afford the desired products (**41**, **42**, and **43**) in 63-76% yields suppressing the competitive homocoupling (see Supplementary Table 11). Notably, in these three cases there was no byproduct formation from pyrimidyl bromide, while very small amount of homodimer product of aryl iodides were obtained (<9% yields). Ortho-substituted aryl halides were also proved to be viable substrates for this protocol, affording the desired products (**43**, **45**, **48**-**50**, **54**) in good yields without any side product formation. Highly reactive functional group such as aldehyde was tolerated in this protocol to afford the desired heterobiaryl **55** in 80% yield. The instability of polyfluoroaryl boronic acids and heteroaryl boronic acids make them a challenging class of substrates for Suzuki-Miyaura cross-coupling reaction. In addition, these boronic acids are generally 5-21 times more expensive as compared to their halide analogue. To our delight, we were successfully able to couple diverse electron-poor and electron-rich heteroaryl halides with polyfluorinated aryl halides in moderate to good yields with excellent cross-selectivity, thereby providing a cost- and step-economic method for the synthesis of polyfluorinated heterobiaryls (**56**-**61**; Fig. 3c). It is important to note that no side products either from heteroaryl halides or polyfluorinated aryl halides were observed.

This cross-electrophile coupling technology was also successful for a range of simple aryl halides. Diverse functional groups including amine, ether, ester, sulfonamide, and cyano groups were well tolerated with this protocol, affording the corresponding unsymmetrical biaryls in synthetically useful yields (**62**-**67**; Fig. 4a). To further demonstrate the potential value of this new versatile catalytic paradigm in medicinal chemistry campaigns, we next sought to achieve a modular synthesis of (hetero)biaryl core of several pharmaceuticals (Fig. 4b). Toward this aim, the biaryl core of Felbinac, Xenbucin (antiarthritic drug), Flufenisal, potent inhibitor of the antiapoptotic protein Bcl-xL, ARB-272572 (PD-L1 inhibitor), Magnolol, Telmisartan, Bifonazole (antifungal drug), A-349821 (histamine H3 receptor antagonist), and CPI-1612 (EP300/CBP histone acetyltransferase inhibitor) were readily synthesized from cheap and commercially available (hetero)aryl halides in reasonable yields (**68**-**76**). This protocol was also effective for the direct synthesis of biaryl containing small molecule drugs such as OTBN (**77**) and Abametapir (**78**). In case of ARB-272572 (**71**), Magnolol (**72**), and Abametapir (**78**), the (hetero)biaryl core was achieved via homo-coupling of corresponding aryl iodide and heteroaryl bromide respectively in excellent yields. Finally, this cross-electrophile coupling technique could be extended to the selective modification of peptides (Fig. 4c). Initial exploration on the coupling of peptide with (hetero)aryl halides using our standard reaction conditions were unsuccessful. However, the use of a solvent combination of CH_3CN and H_2O (CH_3CN:H_2O = 10:1) were effective to provide the desired cross-coupled products in 51-76% yields (**79**-**81**). In case of the coupling of peptide with electron-rich and electron poor heteroaryl bromide, neither protodehalogention nor homodimer products were obtained from any of the partners. Whereas, we observed small amount (20%) of the homodimer formation of iodo peptide as side product in case of coupling with electron-poor aryl bromide (**81**). To the best of our knowledge, this is the first instance of (hetero)arylation reaction of peptide via cross-electrophile coupling at room temperature. Because of the mild reaction conditions, this bioconjugation strategy would open up a new avenue for chemical biologists to modulate biomolecule structure and function in the context of discovery of new drugs, vaccine candidates as well as therapeutics, novel diagnostic and medical tools, and also in the exploration of complex biological processes[44-

[46]. Intrigued by the success of this method for cross-electrophile coupling, we next sought to employ it for the synthesis of a diverse symmetrical bipyridine analogue (Fig. 4d). Gratifyingly, this protocol was found to be effective for affording the symmetrical 5,5'-, 3,3'-, 4,4'-, as well as challenging 2,2'-bipyridines from their corresponding halides in 51-89% yields (**82**-**87**). Importantly, we did not observe protodehalogenation products in any of these cases. The scalability of this method was tested by performing the reaction in 10 mmol scale for the synthesis of **13**, **22**, **40**, and **82** without significant decrease in yields (75%, 69%, 55%, and 80% respectively).

The difference in bond dissociation energy of C(sp^2)–OTf and C(sp^2)–Br/Cl has further led us to implement this technology for the coupling of (hetero)aryl triflates with (hetero)aryl bromides/chlorides (Fig. 5). The initial investigation with an equimolar ratio of heteroaryl triflate and heteroaryl bromide using our optimal reaction coditions afforded very poor yield (4%) of the desired cross-coupled product **88** (see Supplementary Table 12). Interestingly, when we replaced the inorganic base (Cs_2CO_3) with a soluble organic base (DIPEA), the yield of the cross-coupled product was increased to 20% along with a certain extent of homo-coupling product formation from triflate (9% yield). After a thorough optimization of ligands, RuPhos was found to be effective to further improve the yield of **88** to 56% (see Supplementary Table 13). With this combination of ligand and base, the coupling of challenging 2-pyridyl fragment was achieved successfully with a variety of (hetero)aryl halides including those based on indole, benzothiophene, benzofuran, and polyaromatics, albeit in moderate yields (**88**-**95**; Fig. 5a). In addition to 2-pyridyl fragment, simple electron rich aryl triflate could also be coupled with a range of electron deficient aryl bromides (**99**-**102**; Fig. 5b). It is important to note that, in all these cases rest of the starting materials remained unreacted, providing high selectivity towards cross-coupled product formation (only homodimer formation was observed from triflate derivatives in <5% yield). The coupling of activated aryl chloride with (hetero)aryl triflates was also realized using this technique in the presence of a bidentate ligand, XantPhos (**96**-**98**, **101**). We are now working on the design and development of efficient ligand systems to further improve the yield and selectivity of this C(sp^2)–OTf and C(sp^2)–Br/Cl coupling process.

In summary, we have developed a general monometallic catalytic protocol for the synthesis of unsymmetrical (hetero)biaryls directly from (hetero)aryl halides and pseudohalides under mild conditions. The tolerance of this protocol with soluble organic base may overcome considerable challenges for miniaturization and for continuous flow applications posed by inorganic bases in the vast majority of cross-coupling reactions. In addition, the general principle of bond dissociation enthalpy driven synergy of dual palladium catalytic cycle without involving traditional transmetalation step is expected to pave a new horizon in the domain of cross-couplings.

References:

1. Bringmann, G., Günther, C., Ochse, M., Schupp, O. & Tasler, S. Biaryls in Nature: A Multi-Faceted Class of Stereochemically, Biosynthetically, and Pharmacologically Intriguing Secondary Metabolites (Springer-Verlag, New York, 2001).
2. Hajduk, P. J., Bures, M., Praestgaard, J. & Fesik, S. W. Privileged Molecules for Protein Binding Identified from NMR-Based Screening. *J. Med. Chem.* **43**, 3443 (2000).
3. Wu, J. S., Cheng, S. W., Cheng, Y. J. & Hsu, C. S. Donor-Acceptor Conjugated Polymers Based on Multifused Ladder-Type Arenes for Organic Solar Cells. *Chem. Soc. Rev.* **44**, 1113−1154 (2015).
4. Kaes, C., Katz, A. & Hosseini, M. W. Bipyridine: The Most Widely Used Ligand. A Review of Molecules Comprising at Least Two 2,2'-Bipyridine Units. *Chem. Rev.* **100**, 3553–3590 (2000).
5. Hansen, E. C., Pedro, D. J., Wotal, A. C., Gower, N. J., Nelson, J. D., Caron, S. & Weix, D. J. New Ligands for Nickel Catalysis from Diverse Pharmaceutical Heterocycle Libraries. *Nat. Chem.* **8**, 1126−1130 (2016).
6. Meijere, A. D. & Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions* Vol. 1 (Wiley-VCH, ed. 2, 2004).
7. Magano, J. & Dunetz, J. R. Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals. *Chem. Rev.* **111**, 2177−2250 (2011).
8. Brown, D. G. & Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **59**, 4443–4458 (2016).
9. García-Melchor, M., Braga, A. A., Lledós, A., Ujaque, G. & Maseras, F. Computational perspective on Pd-catalyzed C−C crosscoupling reaction mechanisms. *Acc. Chem. Res.* **46**, 2626−2634 (2013).
10. Cox, P. A., Leach, A. G., Campbell, A. D. & Lloyd-Jones, G. C. Protodeboronation of Heteroaromatic, Vinyl, and Cyclopropyl Boronic Acids: pH–Rate Profiles, Autocatalysis, and Disproportionation. *J. Am. Chem. Soc.* **138**, 9145–9157 (2016).
11. Cox, P. A., Reid, M., Leach, A. G., Campbell, A. D., King, E. J. & Lloyd-Jones, G. C. Base-Catalyzed Aryl-$B(OH)_2$ Protodeboronation Revisited: From Concerted Proton Transfer to Liberation of a Transient Aryl Anion. *J. Am. Chem. Soc.* **139**, 13156−13165 (2017).
12. Cook, X. A. F., de Gombert, A., McKnight, J., Pantaine, L. R. E. & Willis, M. C. The 2-Pyridyl Problem: Challenging Nucleophiles in Cross-Coupling Arylations. *Angew. Chem. Int. Ed.* **60**, 11068−11091 (2021).
13. Knapp, D. M., Gillis, E. P. & Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **131**, 6961–6963 (2009).
14. Markovic, T., Rocke, B. N., Blakemore, D. C., Mascitti, V. & Willis, M. C. Pyridine sulfinates as general nucleophilic coupling partners in palladium-catalyzed cross-coupling reactions with aryl halides. *Chem. Sci.* **8**, 4437-4442 (2017).
15. Alberico, D., Scott, M. E. & Lautens, M. Aryl-Aryl Bond Formation by Transition-Metal-Catalyzed Direct Arylation. *Chem. Rev.* **107**, 174−238 (2007).
16. Grover, J., Prakash, G., Goswami, N. & Maiti, D. Traditional and sustainable approaches for the construction of C–C bonds by harnessing C–H arylation. *Nat Commun* **13**, 1085 (2022).
17. Yang, Y. D., Lan, J. B. & You, J. S. Oxidative C-H/C-H Coupling Reactions between Two (Hetero)Arenes. *Chem. Rev.* **117**, 8787−8863 (2017).
18. Zhou, M., Tsien, J. & Qin, T. Sulfur(IV)-Mediated Unsymmetrical Heterocycle Cross-Couplings. *Angew. Chem. Int. Ed.* **59**, 7372−7376 (2020).
19. Hilton, M. C., Zhang, X., Boyle, B. T., Alegre-Requena, J. V., Paton, R. S. & McNally, A. Heterobiaryl Synthesis by Contractive C−C Coupling via P(V) Intermediates. *Science* **362**, 799−804 (2018).
20. Everson, D. A. & Weix, D. J. Crosselectrophile coupling: principles of reactivity and selectivity. *J. Org. Chem.* **79**, 4793–4798 (2014).
21. Hassan, J., Sévignon, M., Gozzi, C., Schulz, E. & Lemaire, M. Aryl−Aryl Bond Formation One Century after the Discovery of the Ullmann Reaction. *Chem. Rev.* **102**, 1359–1470 (2002).
22. Khan, F., Dlugosch, M., Liu, X. & Banwell, M. G. The Palladium-Catalyzed Ullmann Cross-Coupling Reaction: A Modern Variant on a Time-Honored Process. *Acc. Chem. Res.* **51**, 1784–1795 (2018).
23. Chow, W. K., So, C. M., Lau, C. P. & Kwong, F. Y. Palladium-Catalyzed Borylation of Aryl Mesylates and Tosylates and Their Applications in One-Pot Sequential Suzuki−Miyaura Biaryl Synthesis. *Chem. Eur. J.* **17**, 6913−6917 (2011).
24. Molander, G. A., Trice, S. L. J., Kennedy, S. M., Dreher, S. D. & Tudge, M. T. Scope of the Palladium-Catalyzed Aryl Borylation Utilizing Bis-Boronic Acid. *J. Am. Chem. Soc.* **134**, 11667−11673 (2012).
25. Knappke, C. E. I., Grupe, S., Gärtner, D., Corpet, M., Gosmini, C. & von Wangelin, A. J. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem. Eur. J.* **20**, 6828– 6842 (2014).
26. Tang, J.; Liu, L. L.; Yang, S.; Cong, X.; Luo, M.; Zeng, X. Chemoselective Cross-Coupling between Two Different and Unactivated C(Aryl)−O Bonds Enabled by Chromium Catalysis. *J. Am. Chem. Soc.* **142**, 7715−7720 (2020).
27. Ackerman, L.K.G., Lovell, M.M., & Weix, D.J. Multimetallic catalysed cross-coupling of aryl bromides with aryl triflates. *Nature* **524**, 454–457 (2015).
28. Huang, L., Ackerman, L. K. G., Kang, K., Parsons, A. M. & Weix, D. J. LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates. *J. Am. Chem. Soc.* **141**, 10978−10983 (2019).
29. Kang, K., Huang, L. & Weix, D.J. Sulfonate versus sulfonate: nickel and palladium multimetallic cross-electrophile coupling of aryl triflates with aryl tosylates. *J. Am. Chem. Soc.* **142**, 10634–10640 (2020).
30. Kang, K., Loud, N. L., DiBenedetto, T. A. & Weix, D. J. A General, Multimetallic Cross-Ullmann Biheteroaryl Synthesis from Heteroaryl Halides and Heteroaryl Triflates. *J. Am. Chem. Soc.* **143**, 21484−21491 (2021).
31. Wu, T.-F., Zhang, Y.-J., Fu, Y., Liu, F.-J., Tang, J.-T., Liu, P., Toste, F. D. & Ye, B. Zirconium-redox-shuttled cross-electrophile coupling of aromatic and heteroaromatic halides. *Chem* **7**, 1963–1974 (2021).
32. Chuentragool, P., Kurandina, D. & Gevorgyan, V. Catalysis with Palladium Complexes Photoexcited by Visible Light. *Angew. Chem. Int. Ed.* **58**, 11586–11598 (2019).
33. Torres, G. M., Liu, Y. & Arndtsen, B. A. A dual light-driven palladium catalyst: Breaking the barriers in carbonylation reactions. *Science* **368**, 318–323 (2020).
34. Ratushnyy, M., Kvasovs, N., Sarkar, S. & Gevorgyan, V. Visible Light-Induced Palladium-Catalyzed Generation of Aryl Radicals from Aryl Triflates. *Angew. Chem. Int. Ed.* **59**, 10316–10320 (2020).
35. Marchese, A. D., Durant, A. G., Reid, C. M., Jans, C., Arora, R. & Lautens, M. Pd(0)/Blue Light Promoted Carboiodination Reaction-Evidence for Reversible C−I Bond Formation via a Radical Pathway. : *J. Am. Chem. Soc.* **144**, 20554−20560 (2022).
36. Kancherla, R., Muralirajan, K., Maity, B., Zhu, C., Krach, P. E., Cavallo, L. & Rueping, R. Oxidative Addition to Palladium(0) Made Easy through Photoexcited-State Metal Catalysis: Experiment and Computation. *Angew. Chem. Int. Ed.* **58**, 3412–3416 (2019).
37. Luo, Y.-R. Comprehensive Handbook of Chemical Bond Energies (CRC Press, Boca Raton, FL, 2007).

38. Chilamari, M., Immel, J. R., Chen, P.-H., Alghafli, B. M. & Bloom, S. Flavin Metallaphotoredox Catalysis: Synergistic Synthesis in Water. *ACS Catal.* **12**, 4175−4181 (2022).
39. Zhou, W.-J., Cao, G.-M., Shen, G., Zhu, X.-Y., Gui, Y.-Y., Ye, J.-H., Sun, L., Liao, L.-L., Li, J. & Yu, D.-G. Visible-Light-Driven Palladium-Catalyzed Radical Alkylation of C-H Bonds with Unactivated Alkyl Bromides. *Angew. Chem. Int. Ed.* **56**, 15683 –15687 (2017).
40. Martin, R. & Buchwald, S. L. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **41**, 1461–1473 (2008).
41. Kim, S.-H. & Rieke, R. D. 2-Pyridyl and 3-pyridylzinc bromides: direct preparation and coupling reaction. *Tetrahedron* **66**, 3135–3146 (2010).
42. O'Neill, B. T., Yohannes, D., Bundesmann, M. W. & Arnold, E. P. Total Synthesis of (±)-Cytisine. *Org. Lett.* **2**, 4201–4204 (2000).
43. Reichert, E. C., Feng, K., Sather, A. C. & Buchwald, S. L. Pd-Catalyzed Amination of Base-Sensitive Five-Membered Heteroaryl Halides with Aliphatic Amines. *J. Am. Chem. Soc.* **145**, 3323–3329 (2023).
44. Zhang, C., Vinogradova, E. V., Spokoyny, A. M., Buchwald, S. L. & Pentelute, B. L. Arylation Chemistry for Bioconjugation. *Angew. Chem. Int. Ed.* **58**, 4810 – 4839 (2019).
45. Carrico, I. S. Chemoselective modification of proteins: hitting the target. *Chem. Soc. Rev.* **37**, 1423–1431 (2008).
46. Xue, L., Karpenko, I. A., Hiblot, J. & Johnsson, K. Imaging and manipulating proteins in live cells through covalent labelling. *Nat. Chem. Biol.* **11**, 917 – 923 (2015).

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Author contributions

S.M., and D.M. conceived the concept. All authors designed, performed, and analyzed the experiments. D.M. supervised the experimental work. S.M. and D.M. prepared the manuscript.

Competing interests: A patent application has been filed by the Indian Institute of Technology Bombay based on the work described in this manuscript; application number 202321010040. The authors declare no other competing financial interests.

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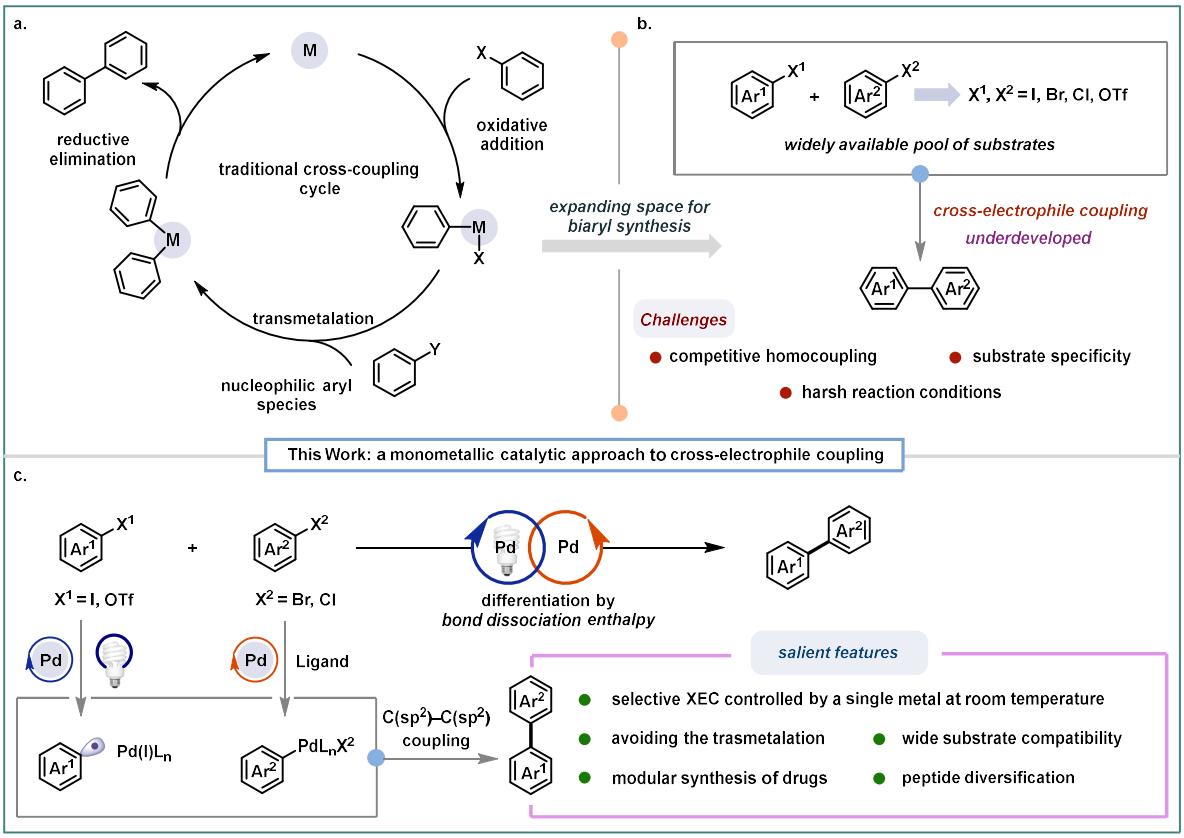
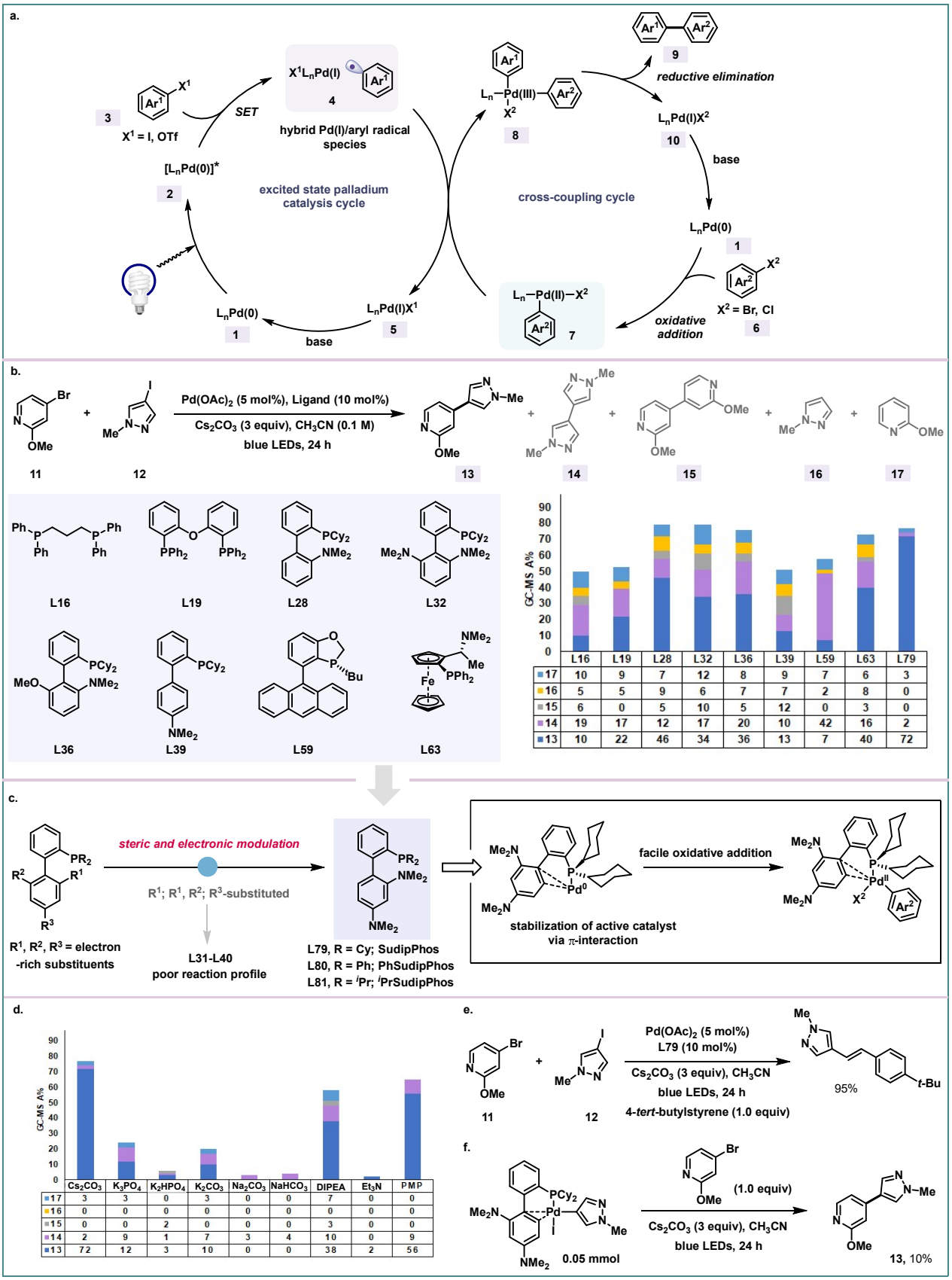


Figure 1 | **C(sp^2)–C(sp^2) cross-electrophile coupling *via* visible light driven Pd catalysis. a,** General mechanism for the traditional cross-coupling. **b,** (Hetero)aryl halides and pseudohalides are the most widely available pool of substrates; however, there are several challenges in pairing them *via* Cross-electrophile coupling (XEC) approach. **c,** A general monometallic catalysis strategy for the cross-electrophile coupling of (hetero)aryl halides and pseudohalides is enabled by the visible light driven palladium catalysis.



	L16	L19	L28	L32	L36	L39	L59	L63	L79
17	10	9	7	12	8	9	7	6	3
16	5	5	9	6	7	7	2	8	0
15	6	0	5	10	5	12	0	3	0
14	19	17	12	17	20	10	42	16	2
13	10	22	46	34	36	13	7	40	72

	Cs_2CO_3	K_3PO_4	K_2HPO_4	K_2CO_3	Na_2CO_3	$NaHCO_3$	DIPEA	Et_3N	PMP
17	3	3	0	3	0	0	7	0	0
16	0	0	0	0	0	0	0	0	0
15	0	0	2	0	0	0	3	0	0
14	2	9	1	7	3	4	10	0	9
13	72	12	3	10	0	0	38	2	56

Figure 2 | Proposed mechanistic hypothesis and evaluation of reaction parameters. a, Mechanistic hypothesis. **b**, Selectivities of this monometallic catalysis with different ligand variation. **c**, Ligand design through experimental optimization. **d**, Selectivities of this monometallic catalysis with different base variation. **e**, Comparative reactivity study of heteroaryl halides. **f**, Stoichiometric reaction with oxidative addition complex of **12**. Optimization experiments were run on 0.1 mmol scale. See Supplementary Information for detailed procedures.

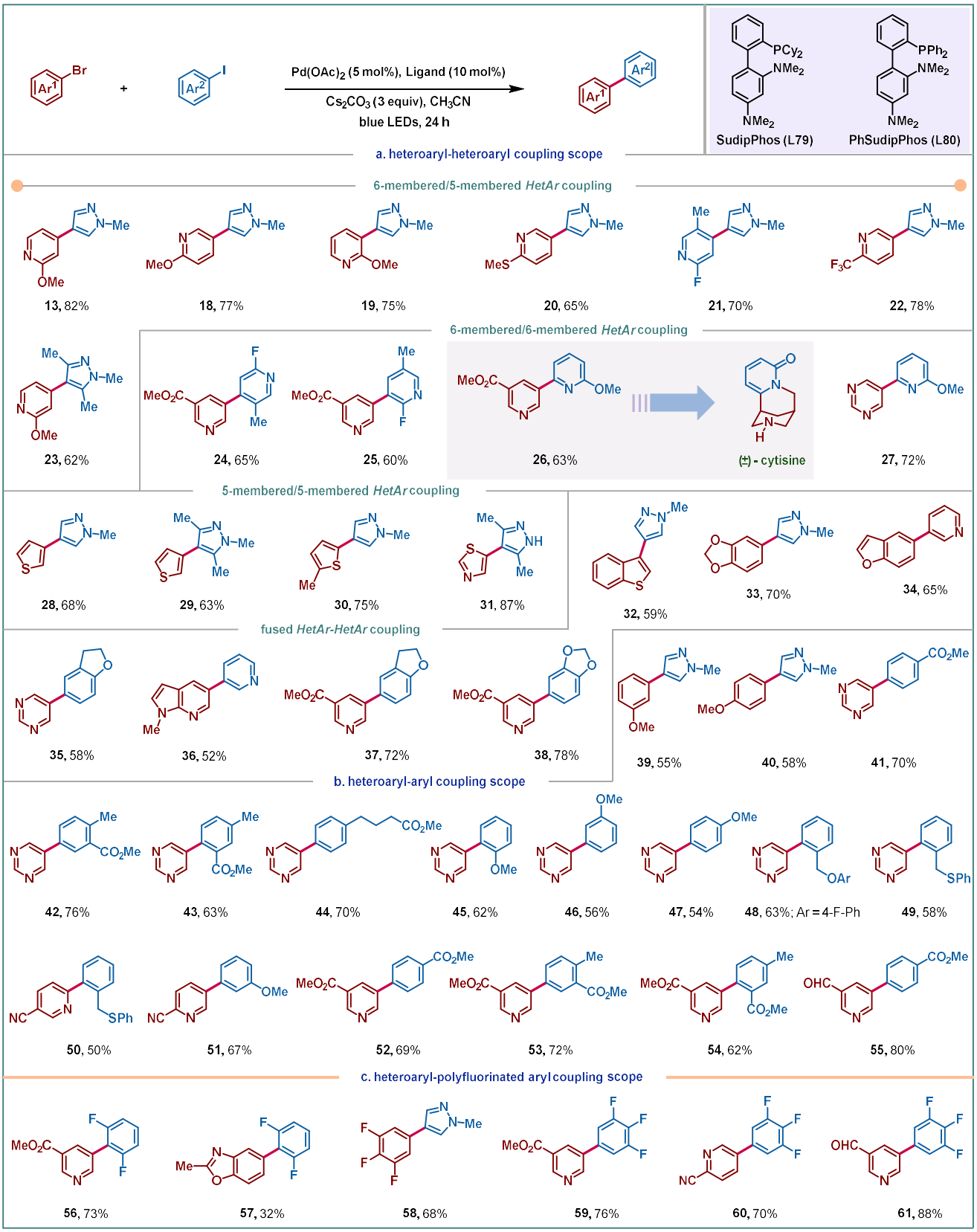


Figure 3 | Scope of XEC of (hetero)aryl iodides with (hetero)aryl bromides. **a**, Scope of heteroaryl-heteroaryl coupling. **b**,Scope of heteroaryl-aryl coupling. **c,** Scope of heteroaryl-polyfluorinated aryl coupling. All yields are isolated. Experiments were typically run on 0.2 mmol scale. See Supplementary Information for exact conditions.

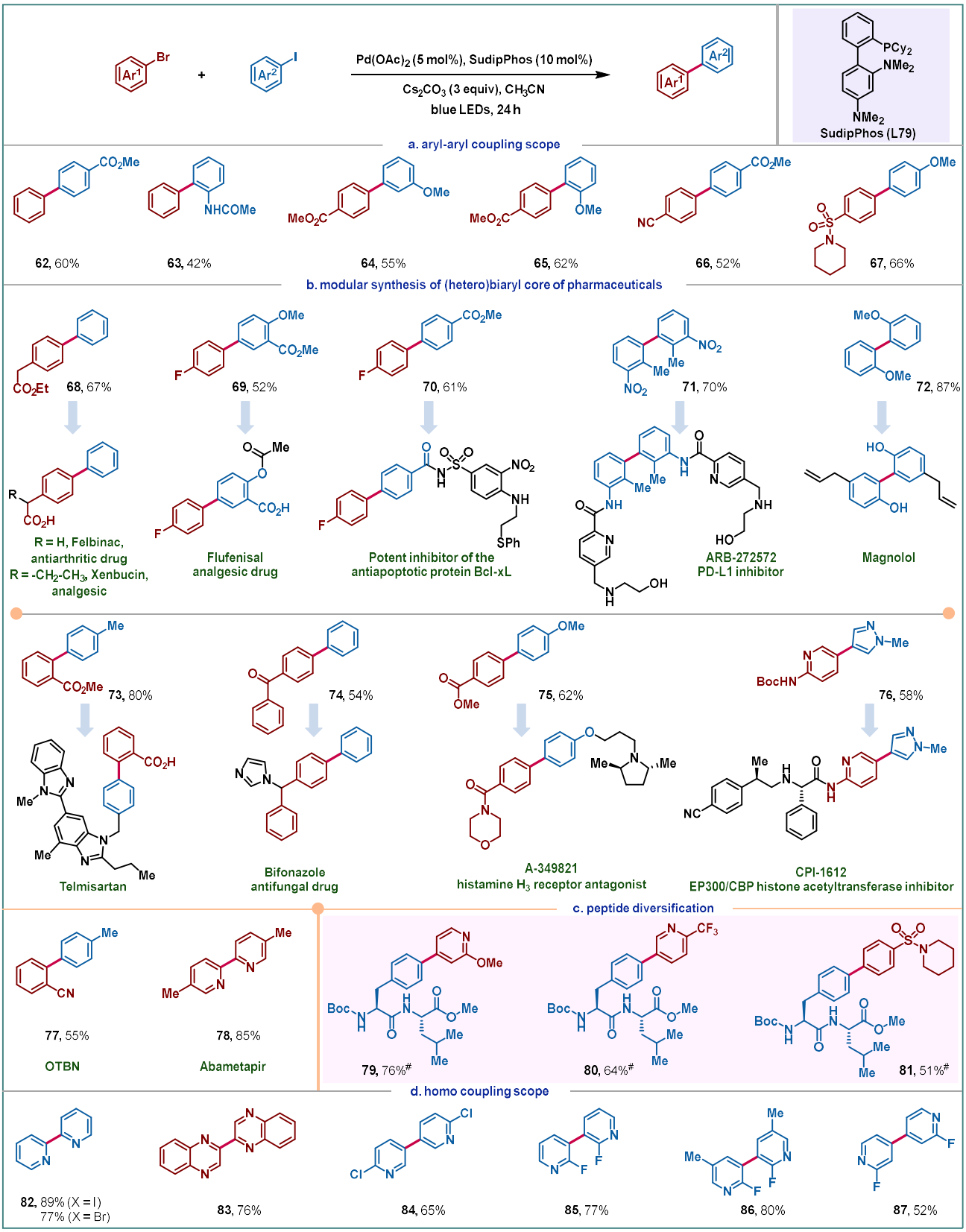


Figure 4 | Scope of XEC of (hetero)aryl iodides with (hetero)aryl bromides. **a**, Scope of aryl-aryl coupling. **b**, This protocol can be applied to the modular synthesis of (hetero)biaryl core of pharmaceuticals. **c,** To demonstrate the applicability of this XEC method in bioconjugation, peptide were evaluated with heteroaryl halides. **d,** Scope of homo-coupling of heteroaryl halides to synthesize a variety of bipyridyl motif. All yields are isolated. Experiments were typically run with 1.0 equiv. of (hetero)aryl iodide, 1.0 equiv. of (hetero)aryl bromide, 5 mol% of $Pd(OAc)_2$, 10 mol% of SudipPhos, 3.0 equiv. of Cs_2CO_3, and 2.0 mL of CH_3CN on 0.2 mmol scale unless otherwise stated. #Solvent combination of CH_3CN and H_2O (10:1) were used and the reactions were done on 0.1 mmol scale. Entries **82-87** has been done by using either heteroaryl iodides or heteroaryl bromides. See Supplementary Information for exact conditions.

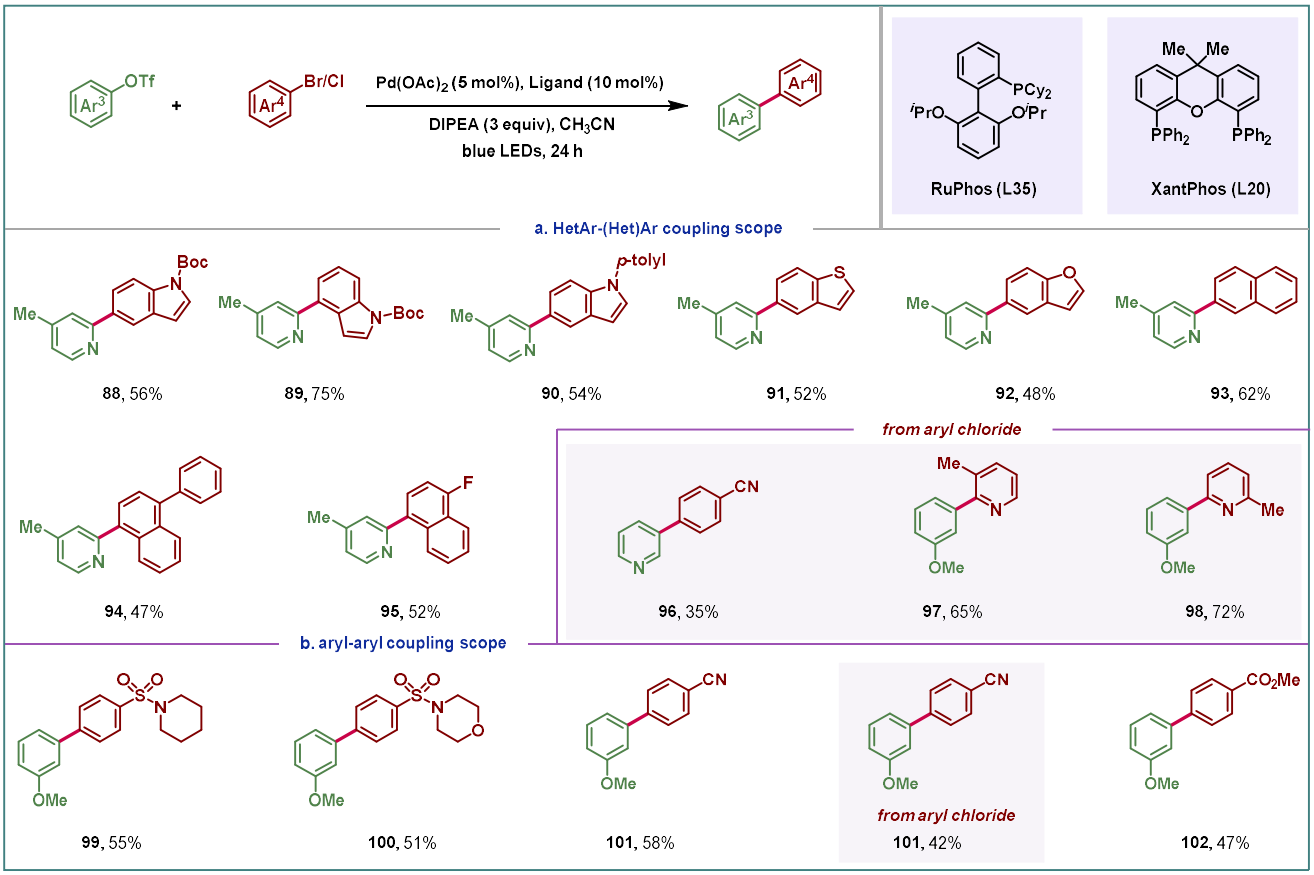


Figure 5 | Scope of XEC of (hetero)aryl triflate with (hetero)aryl halides. **a**, Scope of HetAr-(Het)Ar coupling. **b**, Scope of aryl-aryl coupling. All yields are isolated. Experiments were typically run with 1.0 equiv. of (hetero)aryl triflate, 1.0 equiv. of (hetero)aryl halide, 5 mol% of $Pd(OAc)_2$, 10 mol% of ligand, 3.0 equiv. of DIPEA, and CH_3CN (2.0 mL) on 0.2 mmol scale. The coupling of (hetero)arylbromides with (hetero)aryl triflates were performed using RuPhos as ligand. The coupling of (hetero)arylchlorides with (hetero)aryl triflates were performed using XantPhos as ligand. See Supplementary Information for exact conditions.