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Complementary site-selectivity in arene functionalization enabled by overcoming the *ortho* constraint in palladium/norbornene catalysis

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Achieving site-selectivity in arene functionalization that is complementary to the site-selectivity from electrophilic aromatic substitution reactions has been a long-standing quest in organic synthesis. Palladium/norbornene cooperative catalysis potentially offers a unique approach to this problem, but its use has been hampered by the *ortho* constraint, which is the requirement of an *ortho* substituent for mono *ortho* functionalization of haloarenes. Here, we show that such a challenge could be addressed using a new class of bridgehead-modified norbornenes, thereby enabling a broadly useful strategy for arene functionalization with complementary site-selectivity. A range of *ortho*-unsubstituted aryl iodides, previously problematic substrates, can now be employed to provide mono *ortho*-functionalized products effectively. This method is applicable for late-stage functionalization of complex bioactive molecules at positions that are difficult to reach by conventional approaches.

Undoubtedly, practical and site-selective arene functionalization plays a pivotal role in pharmaceutical, agrichemical and material research. Typically, arene functionalization is realized through electrophilic aromatic substitution (EAS) followed by further *ipso* transformations; thus, the substitution prefers to occur at the more electron-rich and more accessible positions (Fig. 1a). A fundamentally intriguing question is whether complementary and complete site-selectivity can be achieved at positions disfavoured for EAS reactions, such as *para* to an electron-withdrawing group (EWG) or *meta* to an electron-donating group (EDG). The availability of such a technology would greatly enrich our toolbox for streamlining the synthesis of poly-substituted aromatic compounds, which is particularly valuable for late-stage derivatization of complex molecules at positions difficult to reach by conventional means. However, despite the recent breakthroughs of directing group (DG) strategies[1–3] and steric-sensitive C–H borylation/silylation methods[4–8], solutions to such a quest for complementary site-selectivity remain highly sought after.

Palladium/norbornene (Pd/NBE) cooperative catalysis (namely Catellani-type reactions) offers a unique opportunity

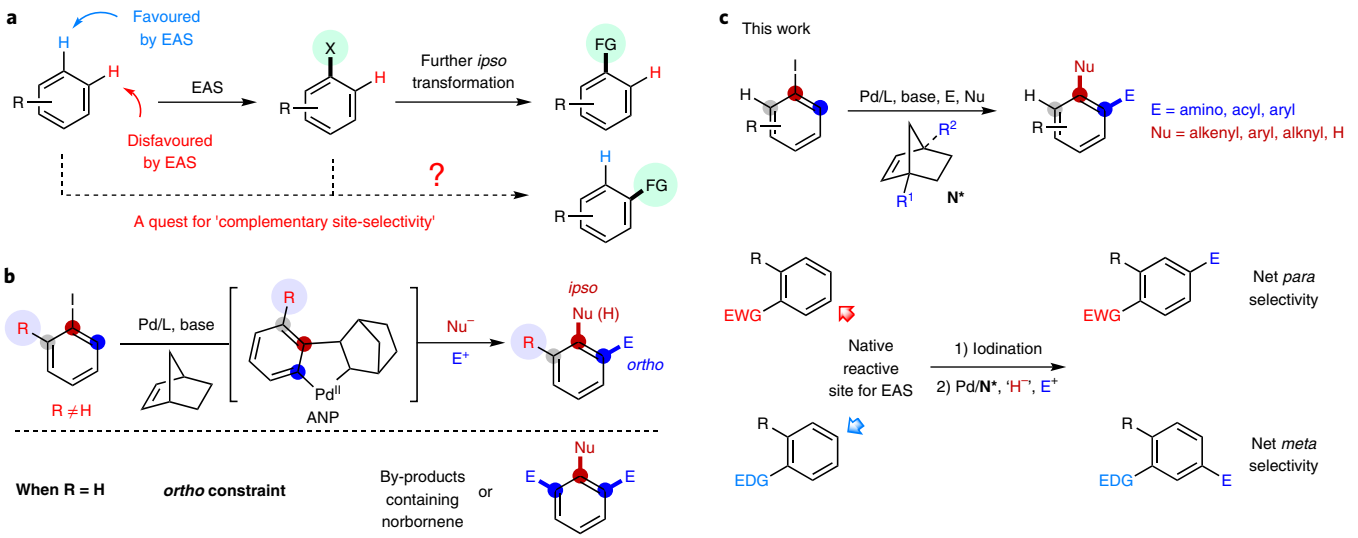

Fig. 1 | A quest for complementary site-selectivity in arene functionalization. a, Site-selective arene C–H functionalization at less reactive positions for EAS is challenging. **b**, Catellani-type reactions can potentially address the challenge, but are inhibited by the *ortho* constraint, which is the requirement of an *ortho* substituent on haloarene substrates to obtain mono *ortho* functionalization. **c**, This work overcomes the *ortho* constraint by developing a new norbornene cofactor, and can be applied towards complementary arene functionalizations.

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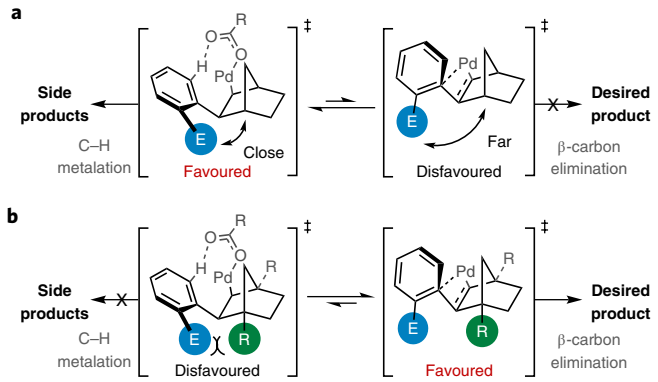


Fig. 2 | Challenge and proposed strategy. a, C–H metallation is favoured over β-carbon elimination with regular NBE. In the C–H metallation TS, the newly installed electrophile is close to the bridgehead position. **b**, β-carbon elimination is expected to be favoured over C–H metallation with a bridgehead-substituted NBE due to the steric repulsion introduced by the **R** group.

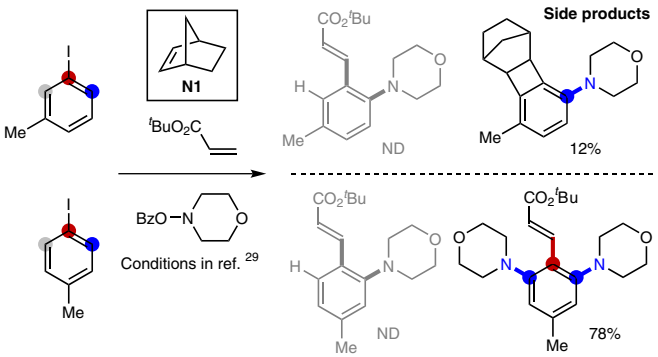
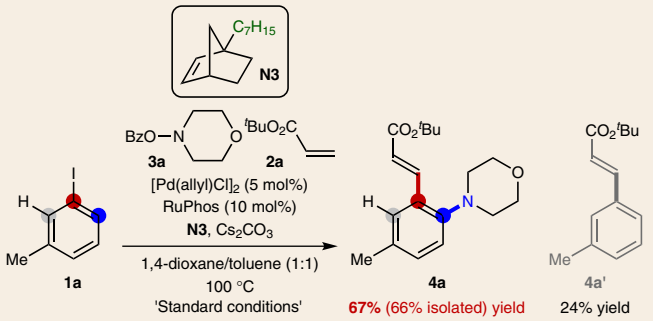


Fig. 3 | An example of the *ortho* constraint. Without *ortho* substituents, 3-iodotoluene and 4-iodotoluene cannot deliver the mono-functionalized products with regular NBE **N1**. 3-Iodotoluene delivered norbornene-containing side products, while 4-iodotoluene only afforded di-amination products. ND, not detected.

to address the above challenge[9–14]. Taking advantage of a key aryl-NBE palladacycle (ANP) intermediate, an electrophile and a nucleophile can be coupled simultaneously to give either *ortho*,*ipso*-bis-functionalization or *ortho*-functionalization when a reductant is used (Fig. 1b)[15–22]. We envisage that electrophilic halogenation of the arene followed by *ortho*-functionalization would install functional groups at positions that are complementary to the outcomes with EAS reactions. Unfortunately, such an approach has been inhibited by a major limitation in Pd/NBE catalysis, the so-called '*ortho* constraint'; when an *ortho*-unsubstituted haloarene is used (for example, *meta*- or *para*-substituted ArXs), mono-*ortho*-functionalization generally cannot be obtained[23,24], and, instead, a complex mixture of NBE-containing side products[19,25,26] or di-functionalization usually dominate (Fig. 1b)[15–17,24,26–38]. Thus, strategies that can overcome such an intrinsic limitation would significantly boost the utility of Pd/NBE catalysis, which in turn would provide a useful strategy for arene functionalization at unactivated sites. Here, we report our development of a new class of NBE 'cofactors' (or co-catalysts) that can enable mono *ortho*-functionalization with *ortho* unsubstituted aryl iodides. The significance of this method is illustrated in the realization of unconventional site-selectivity[35,39,40], such as *para* to an EWG and *meta* to an EDG, through a two-step sequence, as well as site-selective C–H amination of complex bioactive natural products and drugs (Fig. 1c).

Studies by Catellani and co-workers have shown that the challenge of employing *ortho*-unsubstituted aryl iodides arises from a facile second C–H metallation instead of β-carbon elimination, as β-carbon elimination becomes feasible when both *ortho* positions are substituted[9,41]. As shown in Fig. 2, in the transition state (TS) for the C–H metallation with regular NBE, the newly installed electrophile (**E**) must point towards the bridgehead position; in contrast, in the TS for the β-carbon elimination, the aryl-ring plane has to adopt a nearly perpendicular orientation to the bridgehead C–H bond[42,43]. Hence, the key to inhibiting the undesired second C–H metallation and/or promote the β-carbon elimination pathway would be to control the orientation of the arene group during the TS. We hypothesized that by installing a proper substituent (**R**) at the NBE bridgehead (that is, C1 or C4) position, the steric interaction between the **R** and **E** groups (or between the **R** group and the ligand on Pd) would destabilize the TS for the C–H metallation

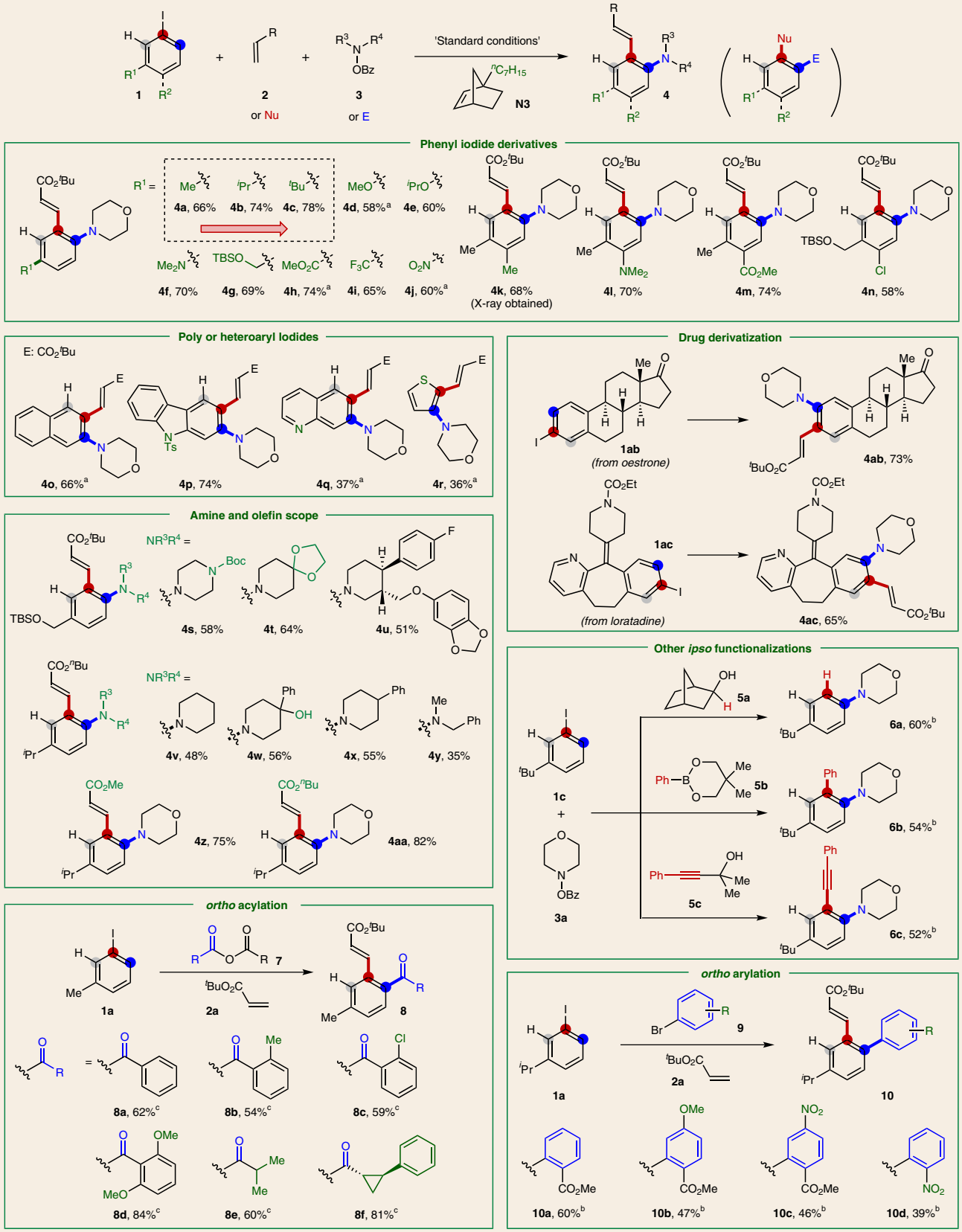
Table 1 | Selected optimization of reaction conditions



Entry	Variations from the 'standard conditions'	Yield of 4a (%)[a]	Yield of 4a' (%)[a]
1	Other NBEs instead of **N3**	Listed below	
	N1: **4a**, <5%; **4a'**, 19%		
	N2: **4a**, 54%; **4a'**, 25%		
	N4: **4a**, 54%; **4a'**, 38%		
	N5: **4a**, 58%; **4a'**, 24%		
	N6: **4a**, <5%; **4a'**, 7%		
	N7: **4a**, 6%; **4a'**, 38%		
	N8: **4a**, 56%[b]; **4a'**, 46%		
2	No Pd	0	0
3	No ligand	6	15
4	No **N3**	0	85
5	$Pd(OAc)_2$ as precatalyst	46	26
6	$P(p\text{-}OMeC_6H_4)_3$ as ligand	15	29
7	K_2CO_3 as base	23	35
8	1,4-Dioxane only	62	20
9	Toluene only	23	22
10	80 °C	50	17
11	10 mol% **N3**	21	58
12	100 mol% **1a**, 110 mol% **2a** and **3a**	46	28

Reaction conditions: **1a** (0.18 mmol), **2a** (0.18 mmol), **3a** (0.1 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), RuPhos (0.01 mmol), **N3** (0.1 mmol), Cs_2CO_3 (0.4 mmol), 100 °C, 24 h. RuPhos: 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl. [a]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]**N8** (0.4 mmol) was used instead.

Table 2 | Reaction scope for *meta*-substituted aryl iodides



Reaction conditions: **1** (0.54 mmol), **2** (0.54 mmol), **3** (0.3 mmol), $[Pd(allyl)Cl]_2$ (0.015 mmol), RuPhos (0.03 mmol), **N3** (0.3 mmol), Cs_2CO_3 (1.2 mmol), 100 °C, 24 h. 12–35% of direct Heck products were observed. TBS, tert-butyldimethylsilyl. [a]**N4** (0.45 mmol) was used instead of **N3**. [b]dppe (0.03 mmol) was used instead of RuPhos. [c]$P(2\text{-furyl})_3$ (0.06 mmol) was used instead of RuPhos. For experimental details and yields of Heck side products, see Supplementary Section V.

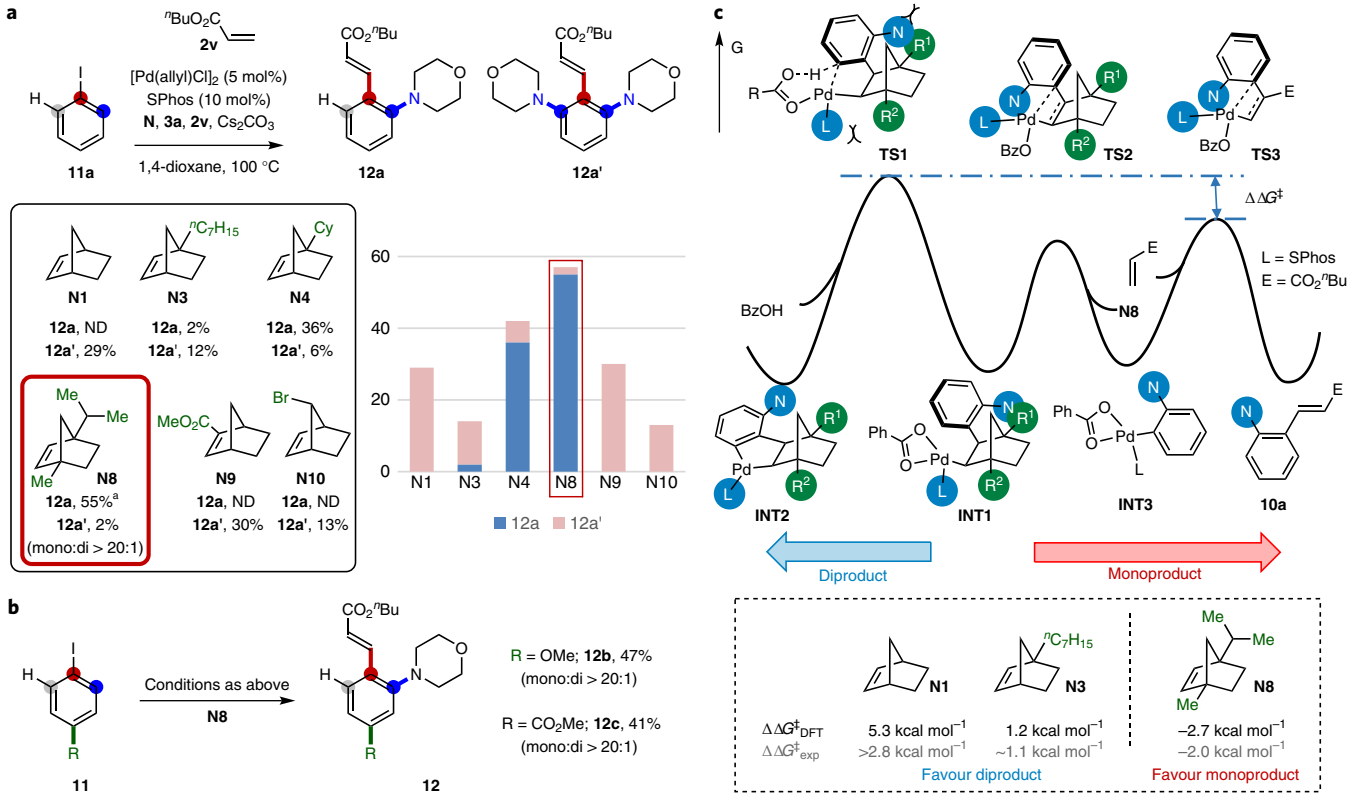


Fig. 4 | Use of *para*-substituted aryl iodides. a, For the more challenging phenyl iodide substrate, examination of different substituted norbornenes reveals that N8 with alkyl substituents at both bridgehead positions gave the highest yield and mono/diselectivity. Reaction conditions: **11** (0.4 mmol), **2v** (0.36 mmol), **3a** (0.2 mmol), $[Pd(allyl)Cl]_2$ (0.01 mmol), SPhos (0.02 mmol), **N** (0.8 mmol), Cs_2CO_3 (0.8 mmol), 100 °C, 24 h. SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; ND, not detected. [a]A yield of 7% was obtained with 10 mol% **N8**. **b**, Examples of other *para*-substituted aryl iodides. **c**, DFT calculation of the key TSs and comparison of calculated and experimental $\Delta\Delta G^{\ddagger}$. Energies were computed at the M06/SDD-6-311+G(d,p)/SMD (1,4-dioxane) level of theory, with geometries optimized at the B3LYP-D3/def2-SVP level (see Supplementary Section IX for more details and references).

pathway due to repulsion, and meanwhile should promote β-carbon elimination by fixing the orientation of the aryl ring (Fig. 2b).

Results and discussion

To test this hypothesis, the *ortho* amination/Heck reaction[29] was chosen as a model. 2-Iodotoluene gave 81% yield of the *ortho* amination product under previously reported conditions, but 3- and 4-iodotoluene were unable to deliver the mono-functionalized products with regular NBE **N1**[29] (Fig. 3). Thus, 3-iodotoluene (**1a**) was used as the initial substrate, and the *ortho* amination was examined with benzoyloxyamine **2a** as the limiting reagent. A number of structurally modified NBEs were prepared and examined (Table 1, entry 1). We envisaged that the size and position of the substituent would be critical, because increasing the steric hindrance of NBE can promote β-carbon elimination, but would also reduce its binding affinity and promote the formation of an undesired direct Heck product (**4a′**). Indeed, NBEs with an alkyl substituent at the bridgehead position (**N2**–**N5**) all effectively provided the desired mono amination product (**4a**) with *n*-heptyl-substituted **N3** being optimal for substrate **1a** (see Supplementary Section III for more detailed discussions and kinetic studies). In contrast, **N4** with a bulkier cyclohexyl group or **N8** with two bridgehead substituents produced more Heck product **4a′**. In addition, ester- or phenyl-substituted **N6** or **N7** only gave a trace amount of **4a**, probably due to a disruptive coordinative interaction with palladium. Note that a survey of ligand effects[17] revealed that RuPhos provided an optimal yield for **1a**, although other ligands, such as 1,2-bis(diphenylphosphino)ethane (dppe) and *N*-heterocyclic carbenes, can also assist this transformation.

The reaction was further optimized with **N3** as the cofactor, and a series of control experiments were conducted to understand the role of each reactant. As expected, the palladium, phosphine ligand and NBE were all essential for this transformation (entries 2–4). $[Pd(allyl)Cl]_2$ was found to be a better precatalyst than $Pd(OAc)_2$ (entry 5). RuPhos is significantly more efficient than the originally reported[28] $P(p\text{-}OMeC_6H_4)_3$ (entry 6), probably benefiting from the bulkiness of the ligand. Consistent with previous studies, the use of potassium carbonate as a base dramatically decreased the yield compared to caesium carbonate (entry 7)[28]. Moreover, a mixed-solvent system is also superior to either 1,4-dioxane or toluene alone (entries 8 and 9), and lowering the reaction temperature decreased the conversion (entry 10). Unsurprisingly, use of 10 mol% of **N3** diminished the yield due to the competing direct Heck reaction, although turnover of **N3** was observed (entry 11). Moreover, on using ArI **1a** as the limiting reagent, the yield decreased to 46% (entry 12).

With the optimized conditions in hand, the scope of iodoarenes was studied first (Table 2). Both electron-rich (**4a**–**4g**) and electron-poor (**4h**–**4j**) aryl iodides are competent coupling partners, which is also evident in the *meta*-, *para*-disubstituted substrates (**4k**–**4m**). With regard to the steric effect, a more sterically hindered *meta*-substituent generally improves the yield (from **4a** to **4c**), probably by inhibiting the second C–H metallation. When substrates contain a small *meta*-substituent (such as a methoxy group), NBE with a

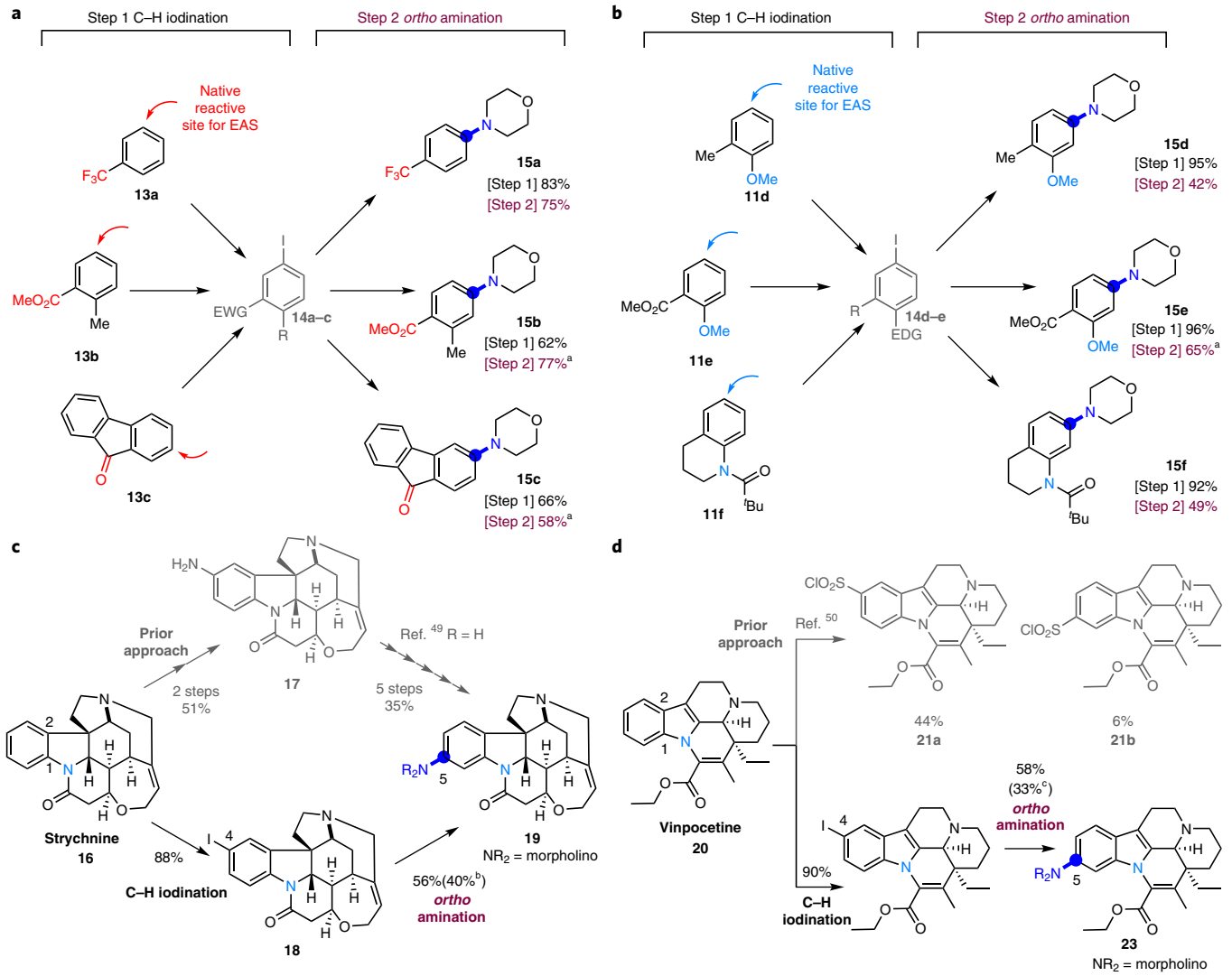


Fig. 5 | Site-selectivity complementary to EAS reactions. a, For arenes with an EWG, functionalization at positions *para* to EWG has been achieved via a sequence of iodination/*ortho* amination, while EAS generally functionalizes *meta* positions. **b**, For arenes with an EDG, functionalization at positions *meta* to EDG has been achieved via a sequence of iodination/*ortho* amination, while EAS generally functionalizes *ortho* or *para* positions. **c**, Amination of strychnine at the C5 position has been realized (the conventional approach required seven steps to achieve the desired site-selectivity). **d**, Amination of vinpocetine at the C5 position was realized (functionalization at the C4 position is usually more common). Reaction conditions: **13** (0.18 mmol), **5a** (0.18 mmol), **3a** (0.1 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), dppp (0.01 mmol), **N3** (0.15 mmol), Cs_2CO_3 (0.4 mmol), 90 °C, 24 h. [a]**N4** (0.2 mmol) was used instead of **N3**. [b]Using **18** (0.1 mmol), **3a** (0.11 mmol) and **5a** (0.11 mmol). [c]Using **22** (0.1 mmol), **3a** (0.11 mmol) and **5a** (0.11 mmol).

bulkier cyclohexyl group (**N4**) was found to be more effective (**4d**). In addition, broad functional group compatibility was observed with tolerance of tertiary amine (**4f**), silyl ether (**4g**), ester (**4h**), nitro group (**4j**) and aryl chloride (**4n**). Heterocycles, such as carbazole, quinoline and thiophene, and naphthalene (**4o**–**4r**) were also suitable substrates. Other amines and olefins were investigated next as coupling partners. A variety of benzoyloxyamines, such as those from protected piperidone, piperidine and Boc-protected piperazine (**4s**–**4x**), were successfully employed, including a complex example derived from paroxetine (**4u**). Benzoyloxyamines based on linear amines also provided the mono amination product albeit in a lower yield (**4y**). Ketal (**4t**) and tertiary alcohol (**4w**) were found to be compatible. Note that the protected piperidone moiety (**4t**) is known to serve as a surrogate for the corresponding free aniline[44]. Furthermore, methyl and *n*-butyl acrylates can also be smoothly coupled at the *ipso* position.

Encouraged by the high chemoselectivity, this mono *ortho* amination method was then explored in a setting with more complex molecules. To our delight, *ortho*-unsubstituted aryl iodides derived from drugs oestrone and loratadine (Claritin) delivered the desired amination products (**4ab** and **4ac**) in good yields, demonstrating the potential for rapid bis-functionalization of pharmaceutically interesting compounds.

To highlight the generality of this strategy, the reaction scope with different quenches at the *ipso* position was investigated. In addition to Heck coupling, preliminary success was obtained with reduction (**6a**)[28], Suzuki (**6b**)[30] or Sonogashira (**6c**)[34,45] quenches to install a hydrogen, aryl or alkynyl group, respectively, at the *ipso* position.

Furthermore, the **N3** cofactor is also effective for mono *ortho* acylation[33,46,47] and *ortho* arylation[48], suggesting broad applicability of the proposed strategy. Interestingly, *ortho* substituents on aryl anhydrides have minimal effects on reactivity (**8b**–**8d**). Both electron-rich (**8d**) and electron-deficient (**8c**) aryl anhydrides worked smoothly, and the alkyl anhydrides also afforded the desired products (**8e**–**8f**). Similar to previous observations[48], aryl bromides with

an *ortho* EWG serve as better electrophiles for the *ortho* arylation reaction (**10a**–**10d**).

We next sought to examine the reaction with *para*-substituted aryl iodides, which is more challenging due to a more facile second C–H metallation[41]. Hence, **N8** with alkyl substituents at both bridgehead positions was synthesized to further inhibit the second C–H metallation (*vide supra*, Fig. 2b). Gratifyingly, using **N8** as the cofactor, simple phenyl iodide (**11a**) indeed gave the desired mono-functionalized product (**12a**) in 55% yield with mono/di selectivity greater than 20:1 (Fig. 4a). Although the efficiency of this preliminary discovery remains to be improved, it is exciting that this result represents the first example for obtaining the mono-functionalized product with *ortho*- and *meta*-unsubstituted aryl iodides using Pd/NBE catalysis. For comparison, regular NBE (**N1**) or NBEs with substituents at other positions (**N9** or **N10**) gave no such product. NBEs with a substituent at one bridgehead position (**N3** or **N4**) also yielded the mono product, albeit with reduced yields and selectivity. Finally, *para*-substituted iodoarenes with either an EDG or EWG still afforded the desired mono products (**12b** and **12c**), thus showing promise for general reactivity (Fig. 4b).

To gain some mechanistic understanding about the critical role of the **N8** cofactor, a computational study using density functional theory (DFT) was performed (Fig. 4c). The key TSs for the second C–H metallation, β-carbon elimination and migratory insertion (Heck quench) steps were compared using phenyl iodide as the model substrate with **N1**, **N3** or **N8** as cofactors. From the common intermediate **INT1** (for a detailed discussion about regioselectivity during the initial migratory insertion step, see Supplementary Section IV), diproduct will be formed through the second C–H metallation (**TS1**), and monoproduct will be formed through β-carbon elimination (**TS2**) and subsequent migratory insertion (**TS3**). Of these, migratory insertion of acrylate **2v** is the rate-limiting step during formation of monoproduct **12a**, thus the selectivity (**12a**:**12a′**) is dictated by the $\Delta\Delta G^{\ddagger}$ between **TS1** and **TS3**. Not surprisingly, C–H metallation (**TS1**) is energetically favoured by 5.3 kcal mol^{-1} with regular NBE **N1**, which is consistent with its inability to form **12a**. On the other hand, using **N3** with one bridgehead substituent, the $\Delta\Delta G^{\ddagger}$ was reduced to 1.2 kcal mol^{-1}. When the sterics were further increased and both bridgehead positions were substituted (**N8**), the kinetic barrier for the C–H metallation step was found to be significantly higher due to the collision of these bridgehead substituents with both the phosphine ligand and the amino group (see Supplementary Section X for details). In contrast, the β-carbon elimination and migratory insertion steps exhibited reduced activation energy, probably caused by easier extrusion of the bulkier NBE.

Finally, a sequence of electrophilic iodination followed by *ortho*-functionalization was demonstrated to install functional groups at positions disfavoured for EAS reactions (Fig. 5). The net transformation allows convenient functionalization of positions *para* to EWGs (**15a**–**15c**) and *meta* to EDGs (**15d**–**15f**). The utility of this approach was further illustrated in the late-stage site-selective derivatization of complex molecules. For example, site-selective amination at the C5 position of strychnine was achieved using this strategy, while the conventional approach required a seven-step sequence[49]. In addition, vinpocetine, a medicine under the brand name Cavinton, can be selectively functionalized at the C5 position (**23**), whereas, under EAS conditions, the C4 position is typically more reactive (**21a** versus **21b**)[50]. Considering the importance of introducing amine moieties in pharmaceutical intermediates, this approach is expected to be valuable for drug discovery.

Conclusions

Through the development of a new class of NBE cofactors that can overcome the longstanding *ortho* constraint in Pd/NBE catalysis, complementary site-selectivity in arene functionalization has been achieved and demonstrated in late-stage derivatization of complex molecules. The sequence of C–H iodination followed by *ortho*-functionalization allows the installation of functional groups at positions disfavoured for EAS reactions, thereby offering a distinct approach to control site-selectivity. The broad substrate scope, excellent functional group tolerance and knowledge obtained in designing NBE cofactors should open the door to the future development of more active/selective catalyst systems with more general applications.

Data availability. The data supporting the findings of this study are available within this paper and its Supplementary Information. Crystallographic data for compound **4k** have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition no. CCDC 1566682. These data can be obtained free of charge from the CCDC (http://www.ccdc.cam.ac.uk/data_request/cif).

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Author contributions

J.W. and G.D. conceived and designed the experiments. J.W. performed experiments. R.L. and Z.D. helped perform the experiments during the revision. J.W. and P.L. performed calculations. J.W. and G.D. co-wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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