Alkene Dicarbofunctionalisation via High-Valent Nickel Catalysis

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Great advances have been made by leveraging high-valent Pd(II)/Pd(IV) catalysis in the areas of C–H activation and alkene difunctionalisation, thus representing a powerful approach for the construction of carbon-carbon and carbon-heteroatom bond. However, the catalytic reactions involving high-valent Ni(II)/Ni(IV) catalysis are largely underdeveloped. Here we report a Ni(II)-catalysed dicarbofunctionalisation of unactivated alkenes via high-valent Ni(II)/Ni(IV) catalysis. This dicarbofunctionalisation protocol provides a highly efficient and direct route towards vicinal substituted alkanes using primary, secondary, and tertiary amides, as well as secondary and tertiary amines as the native directing group under redox-neutral conditions that are challenging to access through conventional methods. The key to the success of this reaction is the use of a bulky *β*-diketone ligand, which could enable the insertion of alkene to aryl-Ni(II) species, stabilize the alkyl-Ni(II) species and inhibit the homolytic alkyl-Ni(II) cleavage. This dicarbofunctionalisation reaction features the use of native directing group, a broad substrate scope, and excellent scalability. The resulting Weinreb amide-derived products can be readily derivatized to a variety of ketones and aldehyde, which are fundamentally useful in synthetic chemistry. In addition, this protocol has been employed for the efficient preparation of several bioactive compounds, showcasing the significant synthetic values of our current method.

Transition metal-catalysed cross-coupling reactions represent indispensable tools for the construction of carbon–carbon bonds and carbon-heteroatom bonds, and have been widely used in both academic and

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industrial settings.[1-4] Although the majority of these processes requires the use of palladium-based catalysts which has revolutionized the way to access complex molecules. Nowadays, chemists are extremely passionate about leveraging nickel catalysts to replace their Pd analogs owing to advantages of being more substantial and economical.[5-9] Recently, one rapidly developing strategy for improving the reactivity, selectivity and scope of this processes is to employ high-valent organometallic palladium intermediates mainly via a Pd(II)/Pd(IV) catalytic cycle[10-13], which has been employed in several hot research areas including C–H activation[14-17], alkene difunctionalisation[18-25] etc. However, the reaction processes via a high-valent Ni(II)/Ni(IV) catalytic cycle remain underdeveloped, which have only been suggested by Kameb and Chatani in Ni-catalysed Grignard cross-coupling[26] and C–H activation reactions[27,28]. The major challenges for developing the Ni(II)/Ni(IV) catalysis might be accounted for the capricious oxidation states (0, +1, +2, +3, +4) of nickel, facile homolytic Ni–C bond cleavage, the higher stability of the open-shell electronic configurations of Ni(I) and Ni(III) species etc (Figure 1a). Despite of those significant challenges, Sanford and others have prepared a series of high-valent Ni(IV) complexes, and demonstrated the $2e^-$ oxidation of Ni(II) to Ni(IV) and reductive elimination on Ni(IV) complex are feasible[29-33], which raises questions about the plausibility of Ni(IV) intermediates in catalytic transformations, similar to their Pd(IV) congeners. Undoubtably, the development of high-valent Ni catalysis via a Ni(II)/Ni(IV) catalytic process will not only offers the advantage of being more economical and efficient than their palladium analogs, but also provide new opportunities for the design and development of adventurous alkene difunctionalisation reactions for increasing the molecular complexity, which can complement or even in some cases supersede existing or related processes operating via Pd(II)/Pd(IV) catalysis. In addition, the development of novel processes based on high valent Ni(II)/Ni(IV) catalysis using the oxidative reagents as the internal oxidant is also an significant complement to the well-known Ni(0)/Ni(II) and Ni(I)/Ni(III) catalysis, which might result in mild redox neutral conditions, a broad substrate scope with redox-active functionalities, compatibility of native functional groups, and the omittance of additional reductants.

Transition metal-catalysed difunctionalisation of alkenes has emerged as a powerful and straightforward strategy for efficient introduction of two functional groups across the double bond within a single operation and the rapid increase in molecular complexity[18-20, 34-43], due to the fact that alkenes are one

of the most readily available raw materials in organic synthesis. In the area of palladium catalysis, the alkene oxidative difunctionalisation has been well established via nucleophilic palladation or carbon-Pd(II) species initiated processes to form alkyl-Pd(II) species, followed by the formation of Pd(IV) intermediates in the presence of various oxidants[18-25] (Figure 1b). Similar to high-valent Pd-catalysed oxidative difucntionalisation of alkenes, we envisioned that nickel-catalysed oxidative difunctionalisation of alkenes could also be feasible through a Ni(II)/Ni(IV) catalytic cycle. As depicted in Figure 1c, the carbon-Ni(II) species, readily generated upon the transmetalation from aryl-Met (Met = B, Sn, Zn *et al*) reagents, can be inserted to the alkene via 1,2-migratory insertion controlled by a combination of Ni catalyst with a proper ancillary ligand. The generated alkyl-Ni(II) species might be oxidized to alkyl-Ni(IV) species in the presence of a proper electrophilic reagent, followed by the reductive elimination to afford the difunctionalisation products. The major challenges for realizing the oxidative difunctionalisation of unactivated alkenes via this high-valent Ni(II)/Ni(IV) catalysis with a suitable oxidative reagent include the low reactivity of unactivated alkenes in the presence of a carbon-Ni(II) species, the inhibition of homolytic cleavage of alkyl-Ni(II) species to form the radical species, the precise control of regioselectivity etc. Here, we disclosed a Ni(II)-catalysed dicarbofunctionalisation of unactivated alkenes using alkyl halides as a mild oxidant and arylboronic acid as the aryl-metal reagent under redox-neutral conditions. The key to the success is the use of a bulky β-diketone ligand, which could stabilize the alkyl-Ni(II) species and inhibit the homolytic alkyl-Ni(II) cleavage. This protocol features a broad substrate scope, excellent functional group and heterocycle tolerance, thus paves a new avenue for the expedient enlargement of molecular complexity in a highly efficient manner. The primary, secondary and tertiary alkenyl amides, as well as secondary and tertiary amines are all suitable substrates for this nickel-catalysed arylalkylation and alkenylalkylation reaction by using weaking coordinated amide and amine functional group as the native directing group. In comparison to the known transition metal-catalysed dicarbofunctionalization of unactivated alkenes[39-56], this novel catalytic process simplifies the use of specific strong monodentate or

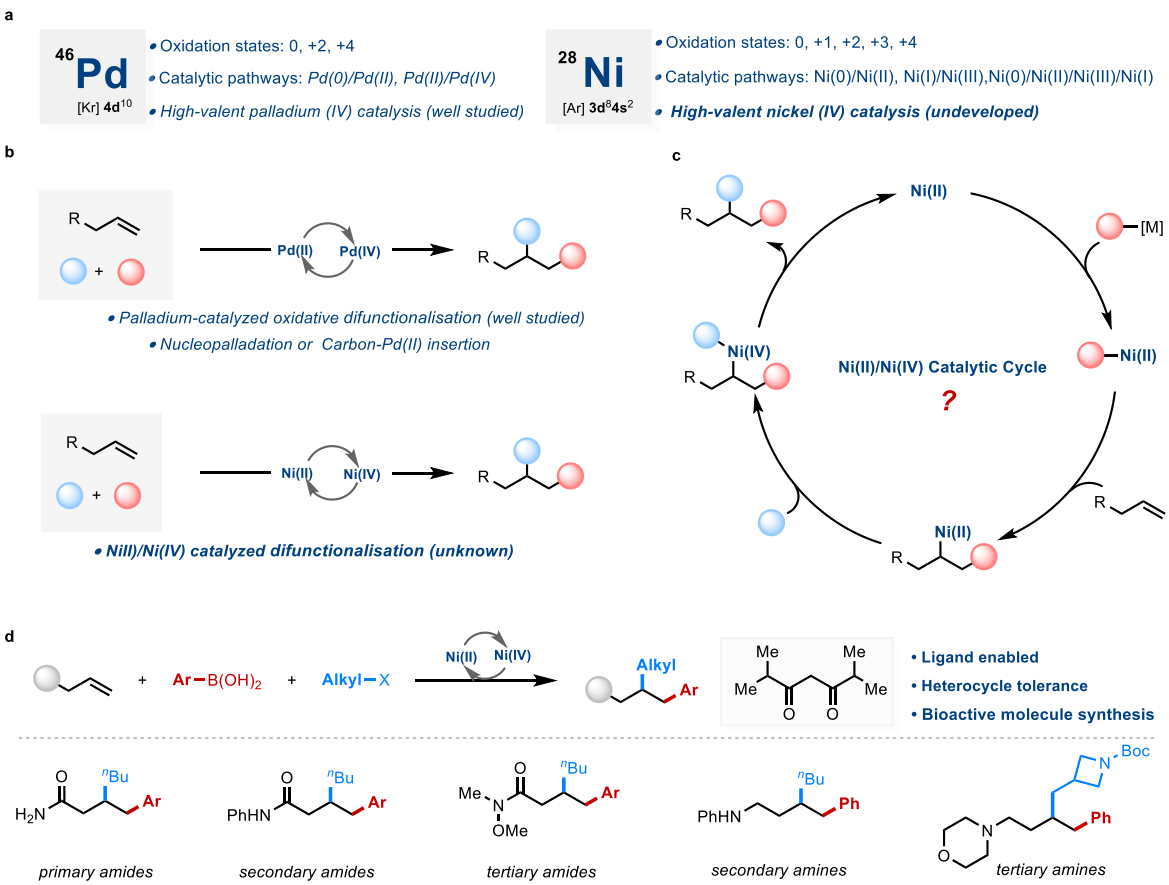

Figure 1 | Synopsis for high-valent nickel catalysis in dicarbofunctionalisation of alkenes. a, Basic characteristics of nickel and palladium. **b**, Pd and Ni catalysed oxidative difunctionalisation of alkenes. **c**, Proposed Ni(II)/Ni(IV) catalytic cycle for difunctionalisation of alkenes. **d**, Ligand-enabled nickel-catalysed dicarbofunctionalisation of unactivated alkenes.

bidentate directing group, representing practical advantages in synthetic applications. Taking advantage of this newly developed process, several bioactive compounds including a CBP/EP300 bromodomain inhibitor, an atypical antipsychotic compound and a key intermediate for the synthesis of potential antipsychotic compound, were prepared in shorter synthetic routes with high step-economy. Preliminary mechanistic studies indicated that this reaction might undergo a novel Ni(II)/Ni(IV) catalytic cycle, which could be applied in the development of numerous high-valent Ni(IV)-involved alkene oxidative difunctionalisation reactions.

Results and discussion

Recently, we have demonstrated a Ni(II)-catalysed hydroxyarylation of unactivated alkenes by using molecular oxygen as the oxidant and oxygen source[57]. Although the reaction mechanism for the oxidation of alkyl-Ni(II) species is unclear, we have proven that the alkyl-Ni(II) species generated by the migratory insertion of alkene into aryl-Ni(II) species is stable in the presence of *β*-diketone ligand, and the radical process via homolytic cleavage of alkyl-Ni(II) species is unlikely. Given the fact that molecular oxygen could oxidize the alkyl-Ni(II) species to alkyl-Ni(IV) species[58,59], we wonder that our Ni(II)-catalysed hydroxyarylation reaction might undergo a Ni(II)/Ni(IV) oxidative process. Following this hypothesis, we attempted to search a suitable mild oxidant for the Ni(II)-catalysed oxidative difunctionalisation reactions with our catalytic system, and found that alkyl halides could serve as a mild oxidant to provide corresponding arylalkylation products by checking the reaction of well-define alkyl-Ni(II) complex with *n*-butyl iodide. The desired alkylated product **S1** was obtained in 30% yield along with the 12% of protonation product **S2** and 5% of dimerized product **S3**. Given the fact that only 5% of low valent Ni species could be formed during the dimerization process and the alkylated product **S1** is largely excess to the low-valent Ni species (30% vs 5%), the large amount of desired alkylated product might be generated by the oxidative process from the alkyl-Ni(II) species rather than a alkyl-Ni(I) species involved process. We hence believe that the Ni(II)-catalysed dicarbofunctionalisation of unactivated alkenes is highly feasible via an oxidative catalytic cycle using alkyl halides as the oxidant and alkylating reagent. Following this lead, we turned to systematically investigate the reaction parameters for catalytic arylalkylation of *β, γ*-unsaturated amides by using phenylboronic acid as the arylating reagent and *n*-butyl iodide as the alkylating reagent. As the ligands play a crucial role in our Ni-catalysed alkene difunctionalisation reactions, we firstly evaluated the ligand effects on this reaction by using $Ni(OTf)_2$ as the catalyst precursor. Not surprisingly, the dinitrogen ligands including bipyridine ligand (**L1**), 1,10-phenanthroline ligand (**L2)**, diimine ligand (**L3**), pyridine-oxazoline (**L4**), bis-oxazoline ligand (**L5**), diamine ligand (**L6**), and NHC ligand (**L7**) didn't afford the desired arylalkylated product. Instead, all those ligands resulted in many side-reactions, including direct Heck-type reaction (**5**), direct isomerization of the unactivated alkene (**6**), hydroarylation (**7**) etc. The use of phosphine ligands including DPPF (**L8**) and DPPH (**L9**), only gave the isomerization products (**6**). These results further confirmed the challenge of the aryalkylation of unactivated alkene without a strong bidentate

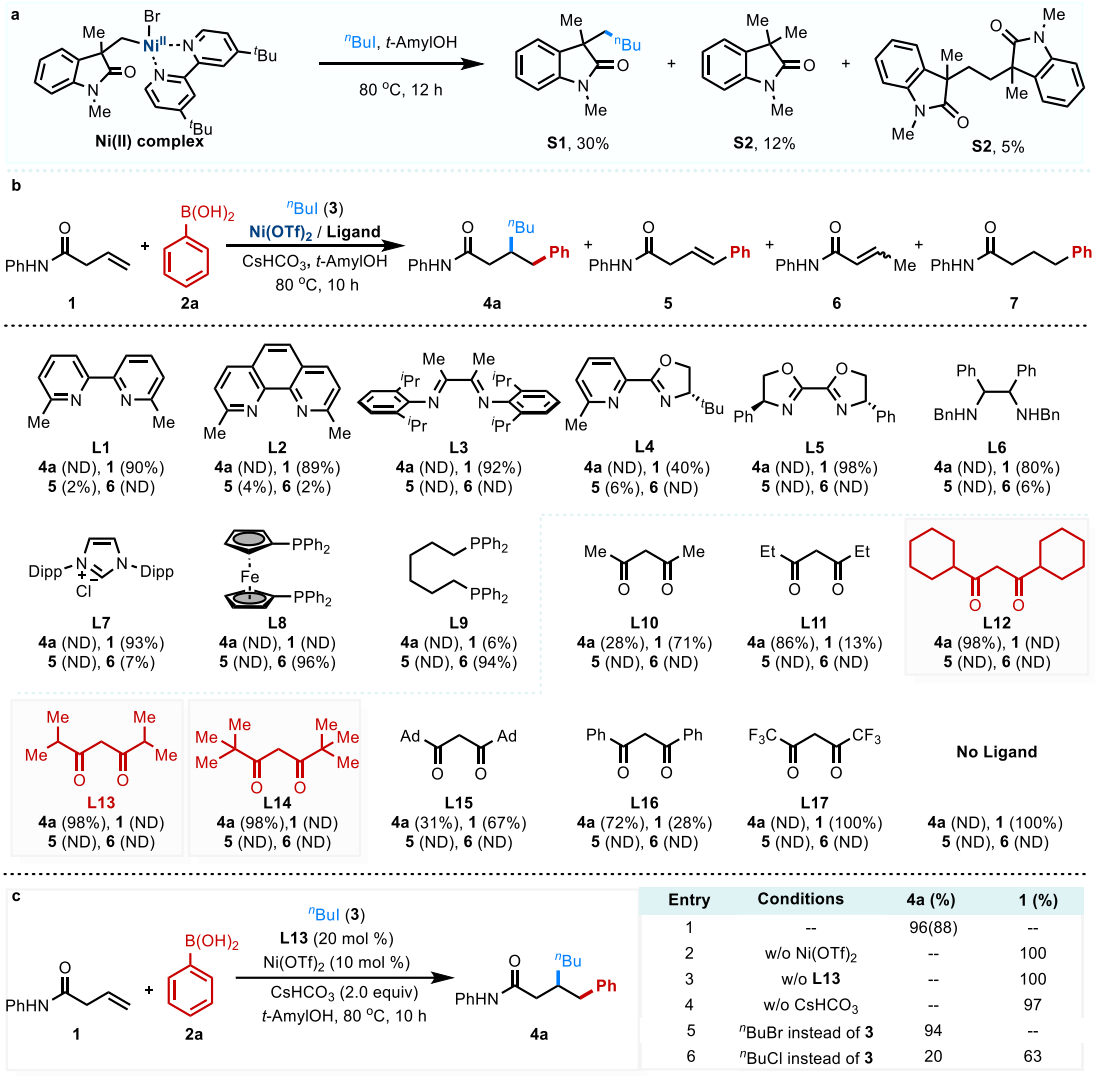

Figure 2 | Ni(II)-catalysed dicarbofunctionalization of unactivated alkenes. a, The reaction of alkyl-Ni(II) complex with *n*-butyl iodide; **b**, Ligand evaluation, the yield was determined by ^{1}H NMR using dibromomethane as the internal standard. See Supplementary Information for experimental details. **c**, Optimal conditions and control experiments. w/o, without.

directing group. Given the bulky *β*-diketone ligands have the capability of promoting the insertion of the Ar-Ni(II) species into unactivated alkenes efficiently[57,60], we next turned our attention to systematically investigate the effects of *β*-diketone ligands. To our delight, the simple acetylacetonate (acac) ligand (**L10**) could provide the desired product in 28% yield, and the efficiency of this reaction could be further enhanced by increasing the steric hindrance on the *β*-diketone ligands (**L11-14**). The diketone ligands bearing cyclohexyl (**L12**), isopropyl (**L13**), *tert*-butyl (**L14**) gave similar reactivities, affording the arylalkylated product in 98% yield. The *β*-diketone ligand bearing 1-adamantyl group (**L15**), which is the optimal ligand in our previous nickel-catalysed hydroarylation reaction[54], resulted in 32% yield. Although

dibenzoylmethane (**L16**) is also reactive for our reaction, electron-deficient hexafluoroacetylacetone (**L17**) did not result in an arylalkylation reaction. Choosing ^{i}Pr-acac ligand (**L13**) as the optimal ligand, the desired product **4a** can be obtained in 88% isolated yield using $Ni(OTf)_2$ as the precatalyst and $CsHCO_3$ as the base in *t*-AmylOH. Control experiments indicated that all reaction parameters were indispensable. Both alkyl bromide and alkyl iodide showed similar reactivities in our protocol, while alkyl chloride was less reactive (Figure 2c).

With the optimized reaction conditions in hand, we set out to evaluate the substrate scope of the ligand-enabled aryalkylation reaction using *N*-phenylbut-3-enamide **1** as the model substrate with *n*-butyl iodide (Figure 3a). Arylboronic acids containing electron-donating or electron-deficient substituent on the *ortho*-, *meta*-, or *para*-position of the aromatic ring served as effective substrates, providing the corresponding products in moderate to excellent yields. Excellent functional group compatibility was observed, and this protocol could tolerate methyl (**2b**, **2l**, **2t**), methoxy (**2c**), trifluoromethoxy (**2d**), fluoro (**2e**, **2n**), chloro (**2f**, **2o**), bromo (**2g**, **2p**), trifluoromethyl (**2h**, **2q**), acetyl (**2i**), ester (**2j**), nitrile (**2k**), methylthio (**2m**). Multisubstituted aryl boronic acids (**2u–y**, **2aa**) and 2-naphthyl boronic acid (**2z**) gave the desired products in 57–83% yields. The arylboronic acid bearing a native phenolic hydroxy group could also be tolerated, providing the arylalkylating product **4r** in 55% yield. Notably, this protocol features excellent heteroatom and heterocycle tolerance, which might find applications in pharmaceutical discovery and synthetic chemistry. For instance, the arylboronic acids bearing morpholine (**2s**), quinoline (**2ab**), benzofuran (**2ac**) and dibenzothiophene (**2ad**) derivatives are all suitable arylating reagents. Notably, the alkenylboronic acids could also been employed in our reaction, giving desired alkenylalkyated products (**4ae**-**4ag**) in 30-63% yields.

Next, we turned our attention to investigate the scope of aliphatic alkyl halides. A wide range of alkyl iodides with various functional groups proceeded smoothly, yielding the desired products in 47-94% yields. The reactions proceeded smoothly in the presence of a methyl (**8a**), long-chain alkyl (**8c**), ester (**8d**), nitrile (**8e**), chloride (**8f**), trifluoromethyl (**8g**), amides with free N-H (**8h**), phthalimide (**8i**), hydroxyl (**8j**), acetal (**8k**), organoboronate (**8l**), phosphate ester (**8m**) to afford the expected products in 57%–94% yield. Notably,

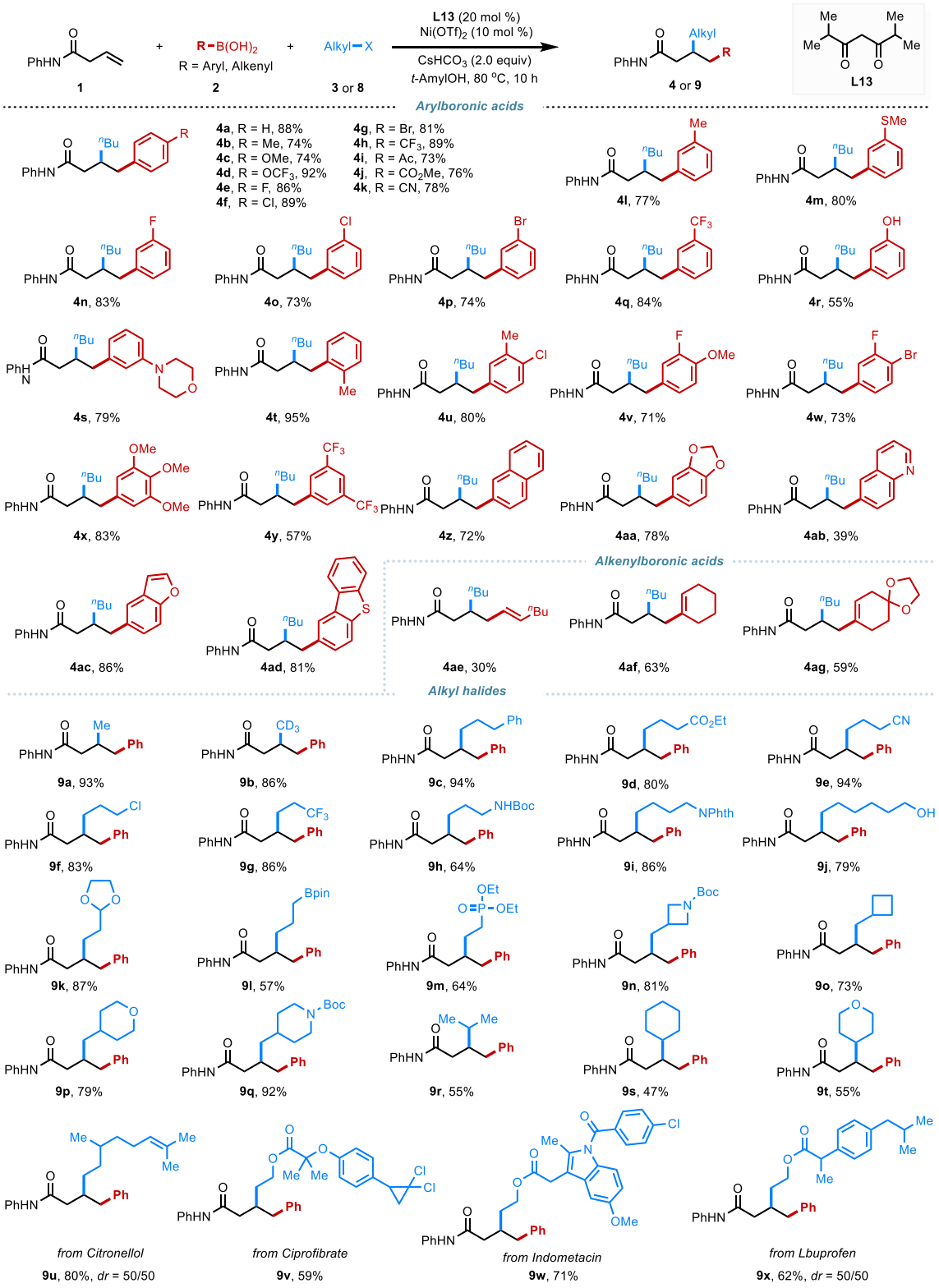

Figure 3 | The scope of arylboronic acids and alkyl halides. The values under each structure indicate isolated yields. Reaction conditions: **1** (35.0 mg, 0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), **3** or **8** (0.4 mmol, 2.0 equiv), $Ni(OTf)_2$ (7.1 mg, 10 mol%), **L13** (6.3 mg, 20 mol%), $CsHCO_3$ (77.6 mg, 2.0 equiv.), *t*-Amyl-OH (1.0 mL), 80 °C, 10 hours. For **9i** and **9j**, alkyl bromides were used.

the deuterated iodomethane can also obtain desired product (**9b**) in 86% yield. Moreover, the alkyl iodides containing heterocycles (**8n**, **8p**, **8q**) were also well-tolerated, obtaining desired products in 79–92% yields. In addition to primary alkyl halides, the secondary alkyl halides (**8r**-**8t**) were also reactive, giving the desired products in moderate yields, albeit the tertiary alkyl halides were not tolerated probably due to the steric hindrance. Bioactive complexes containing alkyl iodides including citronellol (**8u**), ciprofibrate (**8v**), indometacin (**8w**), lbuprofen (**8x**) were well tolerated in our current protocol. We have also investigated aryl halides under our optimal conditions. Unfortunately, no desired diarylated products were formed under current catalytic system, which might be explained by the week oxidative potentials of aryl iodides in comparison to alkyl iodides[31].

The generality of alkenes was evaluated after the scope of arylboronic acids and alkyl halides were systematically evaluated. As listed in Figure 4, various primary, secondary and tertiary amide-substituted unactivated olefins could smoothly be converted to the corresponding arylalkylation products in moderate to high yields. In general, the primary alkenyl amide and secondary alkenyl amides were more reactive than the tertiary alkenyl amides. Both aniline- (**10a**, **10b**) and primary alkyl amine-derived secondary alkenyl amides (**10c-l**) were all suitable substrates, delivering the desired product in 65-98% yields. A variety of functional groups including phenyl (**11c**, **11d**), ether (**11e**), ester (**11f**), Boc-protected amino group (**11g**), indolyl (**11h**), and cyclohexyl (**11i**) were all suitable in this reaction. In comparison to the secondary alkenyl amides, the tertiary alkenyl amides(**10m-p**) gave the desired products with a slightly lower yield (49-74%). It is noteworthy that the Weinreb amide (**10n**) was also compatible with our protocol, affording desired product in 49% yield, which provides a new route for the synthesis of related ketones. This protocol features excellent heterocycle tolerance, the alkenyl amides containing unprotected indole (**10h**), tetrahydro-*2H*-pyran (**10j**), piperidine (**10k**, **10o**), and morpholine (**10p**) were all suitable substrates. The substrates with α-substituents (**10r**, **10s**) were also reactive, giving the desired products in moderate yields. Furthermore, internal alkenes bearing methyl (**10t**) and ethyl (**10u**) at the γ-position could be converted to corresponding products with excellent regioselectivities and diastereoselectivities. A series of bioactive complex molecule-derived alkenyl amides, including aminoglutethimide (**10v**), atomoxetine (**10w**), an apixaban intermediate (**10x**), proved to be compatible with our protocol.

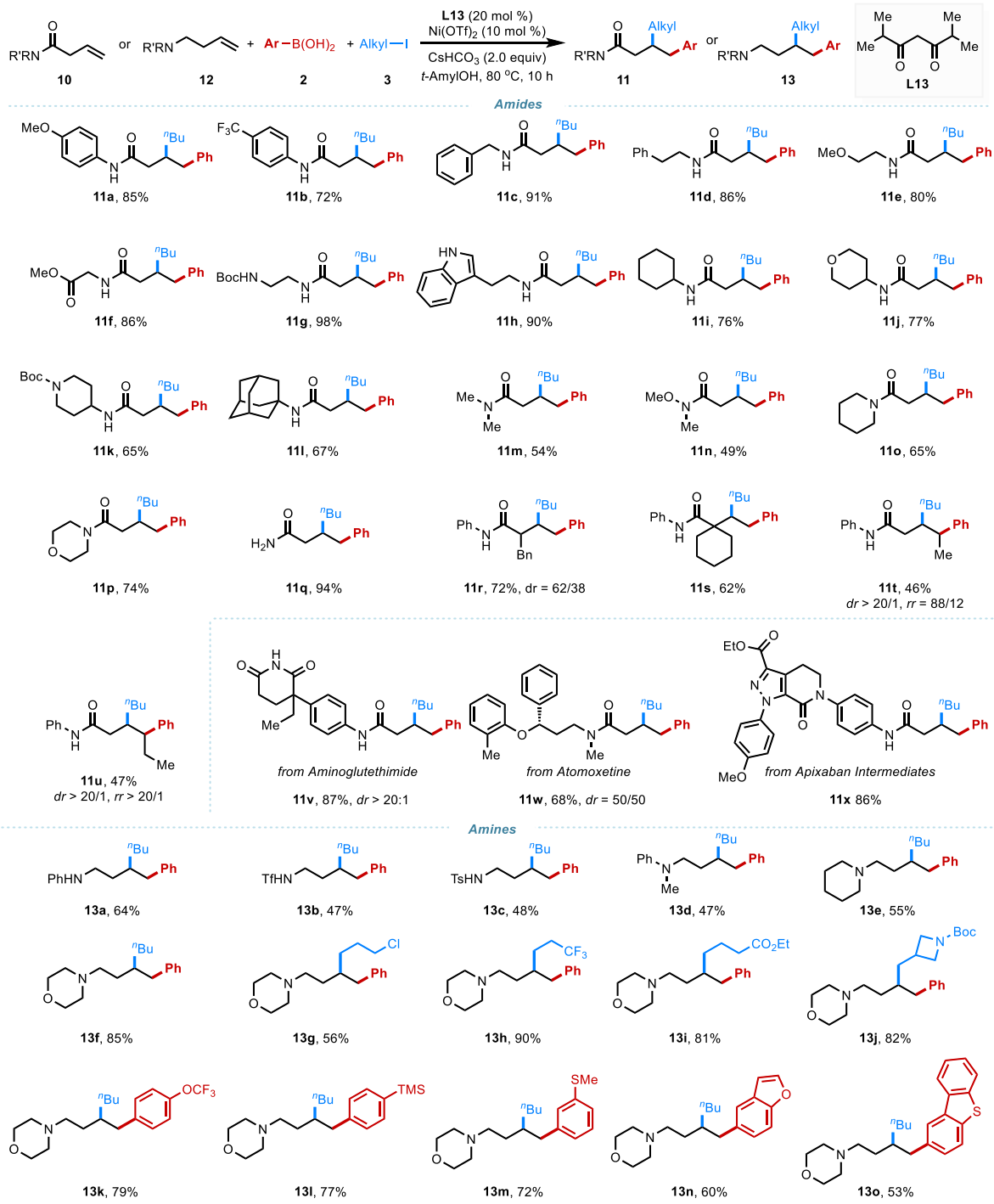

Figure 4 | The scope of unactivated alkenes. The values under each structure indicate isolated yields. Reaction conditions: **10** (35.0 mg, 0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), **3** (0.4 mmol, 2.0 equiv), $Ni(OTf)_2$ (7.1 mg, 10 mol%), **L13** (6.3 mg, 20 mol%), $CsHCO_3$ (77.6 mg, 2.0 equiv.), *t*-Amyl-OH (1.0 mL), 80 °C, 10 hours. For **11t** and **11u**, the reaction was conducted at 90 °C.

Encouraged by the success with alkenyl amides, we envisioned that our protocol could also be applied in other unactivated alkenes bearing other native directing group, such as secondary amines and tertiary amines. To our delight, the secondary alkenyl amine (**12a**) gave the desired arylalkylation product in 64%

yield. Following this positive lead, other secondary amines (**12b-c**) were evaluated, providing the corresponding products in moderate yields. In addition to secondary amines, this reaction possesses excellent compatibility with various tertiary amines, such as *N*-methylaniline (**12d**), piperidine (**12e**), and morpholine (**12f-o**). Again, a large range of alkyl halides (**13g-j**) and aryl boronic acids (**13k-o**) are all tolerate with alkenyl amine substrates with moderate to excellent yields, which highlighted the generality of our newly developed reaction system.

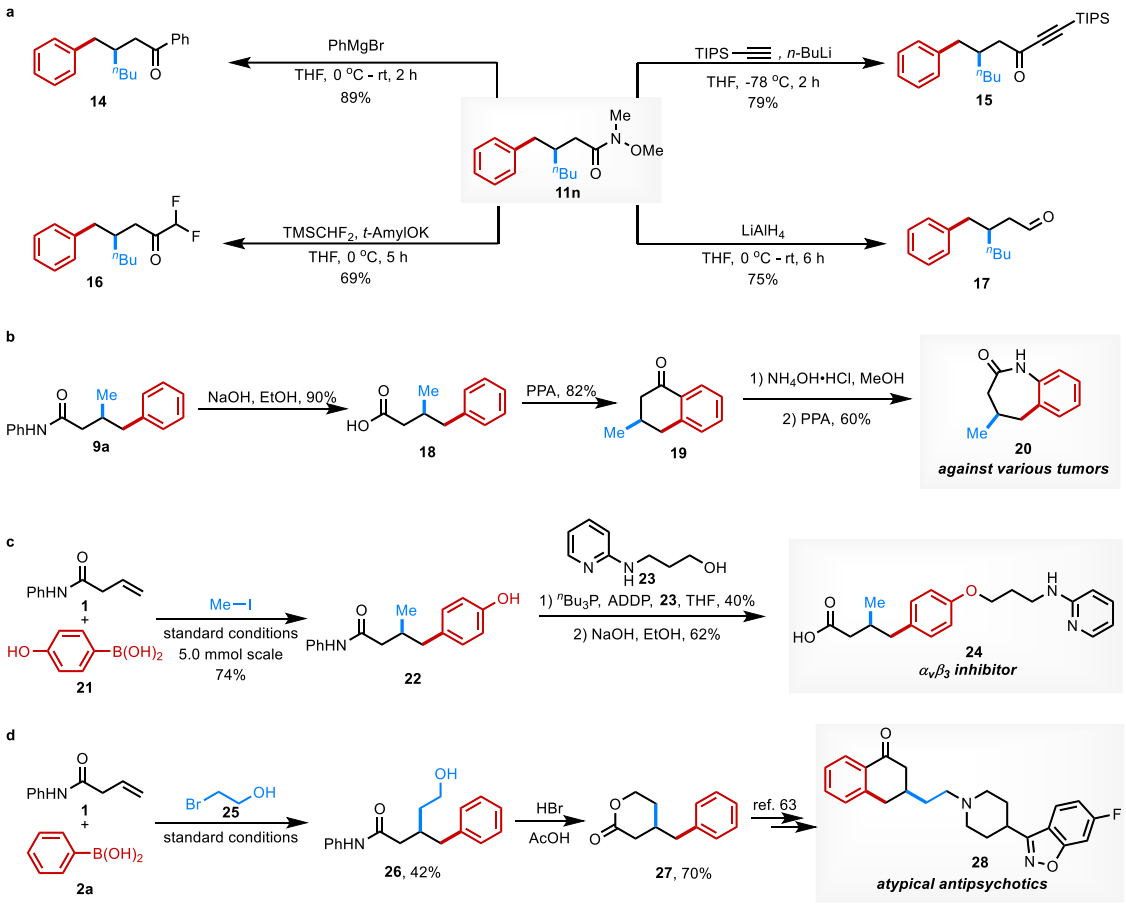

Figure 5 | Derivatization of Weinreb amide and Synthetic Applications. a, Derivatization of the Weinreb amide **11n**. **b,** Synthesis of CBP/EP300 bromodomain inhibitor. **c**, Synthesis of the $\alpha_v\beta_3$ inhibitor. **d**, Formal synthesis of a potential antipsychotic compound. PPA: polyphosphoric acid, ADDP: 1,1'-(azodicarbonyl)-dipiperidine.

To demonstrate the synthetic utility of this newly developed nickel-catalysed dicarbofunctionalization reaction, we preformed synthetic derivatizations employing Weinreb amide derivative **11n.** It is noteworthy that the Weinreb amide is widely utilized in synthetic chemistry and pharmaceutic industry, making it a charming choice for the late-stage derivatization. Treatments of **11n** with various nucleophilic reagents,

including phenylmagnesium bromide, trimethylsilylacetylene in the presence of *n*-BuLi, and $TMSCHCF_2$ in the presence of potassium *tert*-amylate, gave corresponding ketones **14-16** in 69-89% yields. The Weinreb amide could be also converted to the corresponding aldehyde **17** using $LiAlH_4$ as a reductant. To further demonstrate the synthetic utility of this methodology, the efficient synthesis of several bioactive compounds was carried out by using our current method as the key step. For instance, starting from the product **9a**, 4-methyl tetrahydro-*2H*-benzo[*b*]azepin-2-one **20**, a CBP/EP300 bromodomain inhibitor,[61] could be efficiently synthesized via hydrolysis of amide, polyphosphoric acid-facilitated Friedel-Crafts cyclization, condensation with hydroxylamine hydrochloride, and Beckman rearrangement. The $\alpha_v\beta_3$ inhibitor **24** could be efficiently prepared in 3 steps with a synthetic sequence containing arylalkylation of *N*-phenylbut-3-enamide **1** with (4-hydroxyphenyl)boronic acid and methyl iodide, Mitsunobu reaction and further hydrolysis. In comparison to known 6-step synthetic route,[62] this newly established synthetic route is more efficient and concise, showcasing the potential synthetic value of our current method. In addition, the formal synthesis of an atypical antipsychotic **28** could also be achieved by using unmasked 2-bromoethanol **25** as the alkylating reagent, the desired arylalkylated product **26** was generated in 42% yield, which could be transformed to lactone **27** in 70% yield via lactonization in the presence of HBr. Notably, the lactone **27** is the key intermediate for the synthesis of a potential antipsychotic compound[63].

To gain mechanistic insights of this reaction, a series of mechanistic experiments were carried out. The control experiments in the absence of *n*-butyl iodide **3** gave the hydroarylation product **7**, indicating that alkyl halides were not involved in the migration insertion of alkenes to aryl-Ni(II) (Figure 6a). The fact that no arylalkylation products were observed by using alkyl trifluoromethanesulfonate (**29**) instead of alkyl halides under standard conditions, excludes a nucleophilic substitution pathway with in-situ generated alkyl-Ni(II) species and alkyl iodides. As the alkyl-Ni(II) species could undergo a homolytic process to produce alkyl radicals and corresponding Ni(I) species, we next carried out the radical capturing experiments to explore if our reaction might undergo a metal-radical relay process.[64,65] The addition of radical scavenger BHT and TEMPO could not shut down the reaction, providing the desired product in 85% and 32% yield, respectively (Figure 6b). In addition, the reactions with 1,1-diphenylethylene (**30**) or (*E*)-(2-(phenylsulfonyl)vinyl)benzene (**32**) instead of *n*-butyl iodide only resulted in the hydroarylation product

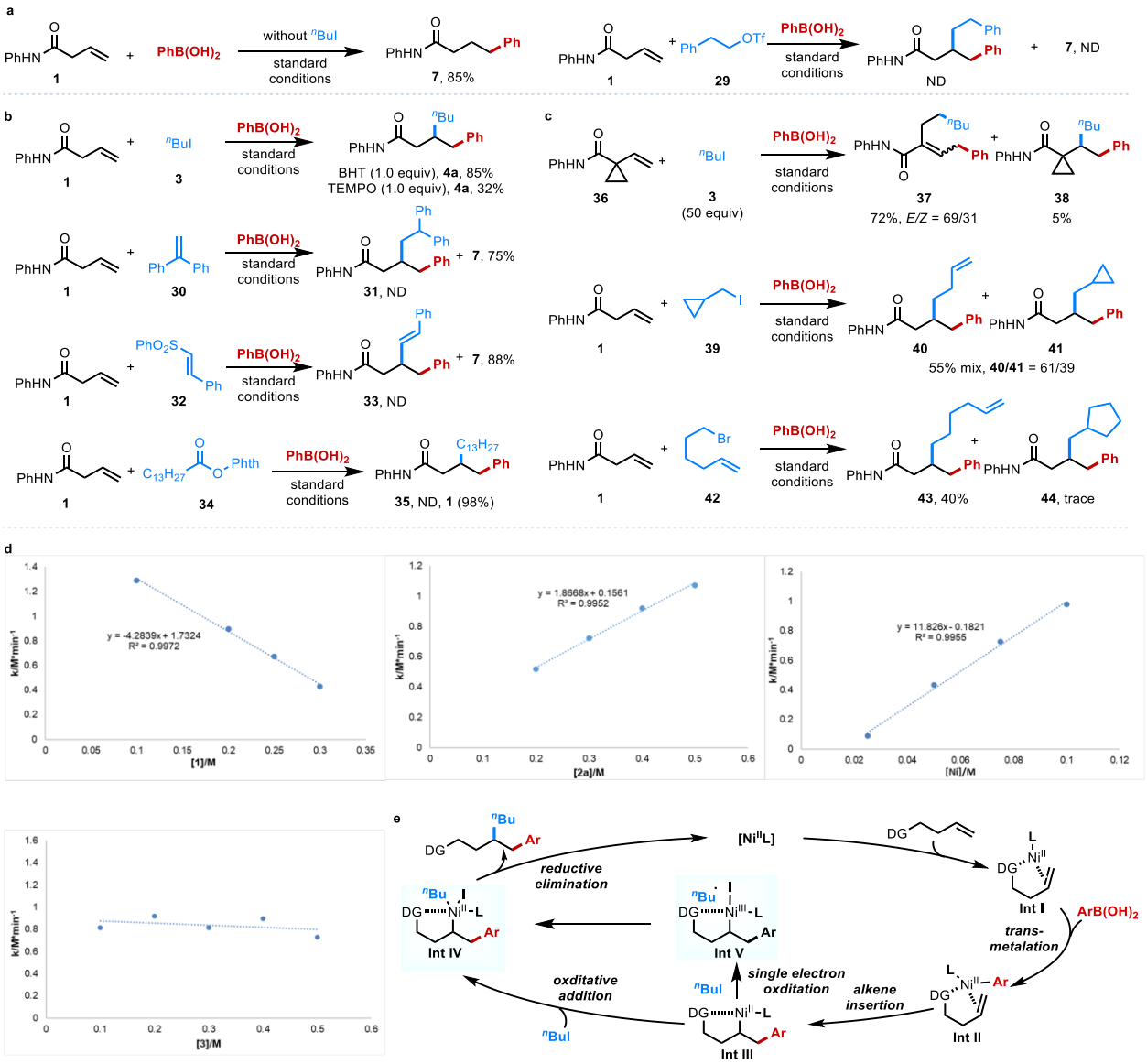

Figure 6 | Mechanistic Studies. a, Control experiments. **b**, Radical trapping experiments. **c**, Radical clock experiments. **d**, Kinetic experiments. **e**, Proposed Ni(II)/Ni(IV) catalytic cycle.

7 in high yield, rather than the formation of arylalkenylation product (**31** or **33**). This control experiment might also imply that the Ni(I)/Ni(II)/Ni(III) mechanism is unlikely in our reaction. Given those substrates are reactive in Ni-catalysed 1,1-arylalkylation of alkenes using bipyridine-type ligand via organometallic-radical relay,[56] these experiments suggested that our reaction might not involve a radical process and our *β*-diketone ligand might be capable of stabilizing the alkyl-Ni(II) species and inhibiting the homolytic alkyl-Ni(II) cleavage. In addition, replacement of alkyl halides with redox-active ester **34** resulted in no reaction, which further indicated the Ni-catalysed coupling via single-electron pathway is unlikely to be involved in

our bulky β-diketone ligand-enabled dicarbofunctionalisation process, given the coupling of redox active ester with Ni(I)/Ni(II)/Ni(III) process is feasible and widely proposed in the literature[66]. Although the radical clock experiment with vinyl cyclopropylamide (**36**) mainly gave the ring-opening product **37** in 72% yield, the observation of the 1,2-arylalkylation product **38** (5% yield) further supports that the free alkyl radical species might not be involved in our reaction (the ring-opening rate of cyclopropylcabinyl radical is 1.3×10^8 s^{-1})[67]. The ring-opening product **37** might be formed though the β-carbon elimination of corresponding alkyl-Ni(II) species (Figure 6c). Notably, the in-situ EPR experiment was carried out with our catalytic system, no EPR signal was observed, which further complies our hypothesis that the Ni(I) and Ni(III) species are not involved in our reaction (See Supplementary Figure S5).

Starting from the alkyl-Ni(II) species, the arylalkylating product **38** could be formed by two-electron oxidation pathway or single electron pathway. To further clarify this process, we next performed the reaction with 6-bromo-1-hexene **42** as an alkylating reagent under standard conditions, which could only provide the arylalkylation product **43** without the formation of radical cyclization products **44** (the rate constant for the rearrangement of 5-hexene radicals to cyclopentyl methyl radicals is 1.0×10^5 s^{-1})[67]. These results might indicate that the formation of high-valent Ni(IV) species via two-electron oxidative addition process is feasible. To further understand this process, the reaction with (iodomethyl)cyclopropane (**39**) was carried out, which afforded a 61:39 mixture of the ring-opening product **40** and cyclopropylmethylated **41** in 55% total yield. The observation of both ring-opening product and normal alkylated product indicated that the alkyl-Ni(II) species might be oxidized by alkyl iodide through both single electron and two-electron oxidation.

Preliminary kinetic studies were also carried out to shed light on the roles of each component (alkene **1**, arylboronic acid **2a**, alkyl iodide **3** and nickel catalyst). Results shown in Figure 6d indicate that this reaction is first order rate dependence on both arylboronic acid and Ni catalyst. Moreover, altering the concentration of alkyl iodide had no significant effect on the reaction rate. Along with the increase of the concentration of alkene, the rate gradually decreases. These kinetic experiments unveiled that the transmetalation step might be the rate determining step in the catalytic cycle. The apparent negative rate

dependence on alkene concentration could be rationalized by the onset of competitive coordination to the intermediate alkyl-nickel species. Based on aforementioned mechanistic studies, we speculate that the reaction may undergo Ni(II)/Ni(IV) catalytic cycle, as depicted in Figure 6e. Firstly, the intermediate **Int I** was obtained by coordinating the olefin with the nickel catalyst, which underwent transmetalation with the arylboronic acid to deliver an Ar–Ni(II) species **Int II**. The alkyl-Ni(II) species **Int III** could be efficiently formed by alkene migratory insertion with the **Int II**. Next, the alkyl-Ni(II) with alkyl iodine underwent oxidative addition to produce the high-valent alkyl-Ni(IV) species **Int IV** which could also be obtained by single-electron oxidation of alkyl-Ni(II) and *n*-butyl iodine (via **Int V**).[65] Finally, reductive elimination of the high-valent alkyl-Ni(IV) species gave the arylalkylated products and regenerated the Ni(II) catalyst.

In conclusion, a nickel-catalysed dicarbofunctionalisation of unactivated alkenes has been achieved via high-valent Ni(II)/Ni(IV) catalysis. The key to achieve this general arylalkylation is the identification of bulky *β*-diketone ligands, which are capable of stabilizing the in-situ generated alkyl-Ni(II) species and inhibiting the homolytic cleavage. The development of high-valent Ni catalysis via a Ni(II)/Ni(IV) catalytic process opens tremendous opportunities for the design of novel alkene difunctionalisation reactions via nickel-catalysed oxidative process. Developing other oxidative difunctionalisation reactions of alkenes via high-valent Ni(II)/Ni(IV) catalysis is ongoing in our laboratory.

Methods Summary

General procedure for Ni-catalysed arylalkylation of alkenes. In a nitrogen-filled glovebox, substrate **1** or **10** or **12**(0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), **3** or **8** (0.4 mmol, 2.0 equiv), $Ni(OTf)_2$ (7.1 mg, 10 mol %), **L13** (6.3 mg, 20 mol %), $CsHCO_3$ (77.6 mg, 0.4 mmol, 2.0 equiv) were charged in a 10-mL tube. The tube was sealed using an open-top cap with PTFE cap liner, and moved outside of the glovebox, followed by the addition of *tert*-amyl alcohol (1.0 mL) under nitrogen atmosphere. The tube was sealed again with parafilm and heated to 80 °C for 10 h. After cooling to room temperature, the mixture was passed through a pad of silica gel with EtOAc as the eluent to remove the nickel and the insoluble precipitate. The

resulting solution was concentrated. The residue was then purified by silica gel chromatography or preparative thin-layer chromatography to afford the arylalkylated product. *Notes: this reaction is sensitive to air and humidity*. Full experimental details and characterization of new compounds can be found in Supplementary Information.

References

1. Meijere, A. D. & Diederich, F. (eds) Metal-Catalyzed Cross-Coupling Reactions (Wiley-VCH, 2004).
2. Magano, J. & Dunetz, J. R. Large-Scale Applications of Transition Metal-Catalyzed Coupling for the Synthesis of Pharmaceuticals. *Chem. Rev.* **111**, 2177−2250 (2011).
3. Jana, R., Pathak, T. P. & Sigman, M. S. Advances in Transition Metal (Pd, Ni, Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev*. 111, 1417–1492 (2011).
4. Meijere, A. D., Bräse, S. & Oestreich, M. (eds) Metal-Catalyzed Cross-Coupling Reactions and More (Wiley-VCH, 2014).
5. Han, F.-S. Transition-Metal-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions: a Remarkable Advance from Palladium to Nickel Catalysts. *Chem. Soc. Rev*. **42**, 5270–5298 (2013).
6. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature*, **509**, 299−309 (2014).
7. Ananikov, V. P. Nickel: The "Spirited Horse" of Transition Metal Catalysis. *ACS Catal*. **5**, 1964−1971 (2015).
8. Hazari, N., Melvin, P. R. & Beromi, M. M. Well-defined Nickel and Palladium Precatalysts for Cross-Coupling. *Nat. Rev. Chem*. **1**, 0025 (2017).
9. Chernyshev, V. M. & Ananikov, V. P. Nickel and Palladium Catalysis: Stronger Demand than Ever. *ACS Catal*. **12**, 1180−1200 (2022).
10. Muñiz, K. High-Oxidation-State Palladium Catalysis: New Reactivity for Organic Synthesis. *Angew. Chem. Int. Ed*. **48**, 9412–9423 (2009).

11. Xu, L.-M., Li, B.-J., Yang, Z. & Shi, Z.-J. Organopalladium(IV) chemistry. *Chem. Soc. Rev*. **39**, 712–733 (2010).

12. Byers, P. K., Canty, A. J., Skelton, B. W. & White, A. H. Oxidative Addition of Iodomethane to [$PdMe_2$(bpy)] and the X-ray Structure of the Organopalladium(IV) Product fac-[$PdMe_3$(bpy)I] (bpy = 2, 2'- bipyridyl). *J. Chem. Soc. Chem. Commun*.1722–1724 (1986).

13. Hickman, A., Sanford, M. High-Valent Organometallic Copper and Palladium in Catalysis. *Nature* **484**, 177–185 (2012).

14. Lyons, T. & Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev*. **110**, 1147−1169 (2010).

15. Engle, K. M., Mei, T.-S., Wang, X. & Yu, J.-Q. Bystanding F^+ Oxidants Enable Selective Reductive Elimination from High-Valent Metal Centers in Catalysis. *Angew. Chem. Int. Ed*. **50**, 1478−1491 (2011).

16. He, J., Wasa, M., Chan, K. S. L., Shao, Q. & Yu, J.-Q. Palladium-Catalyzed Alkyl C-H Bond Activation. *Chem. Rev*. **117**, 8754−8786 (2017).

17. Topczewski, J. T. & Sanford, M. S. Carbon–hydrogen (C–H) bond activation at Pd^{IV}: a Frontier in C–H functionalization catalysis. *Chem. Sci*. **6**, 70–76 (2015).

18. Jacques, B. & Muñiz, K. Palladium Catalysis for Oxidative 1,2-Difunctionalization of Alkenes. Catalyzed Carbon-Heteroatom Bond Formation; John Wiley & Sons, Ltd., pp 119−135 (2010).

19. McDonald, R. I., Liu, G. & Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev*. **111**, 2981−3019 (2011).

20. Yin, G. Mu, X. & Liu, G. Palladium (II)-Catalyzed Oxidative Difunctionalization of Alkenes: Bond Forming at a High-Valent Palladium Center. *Acc. Chem. Res*. **49**, 2413−2423 (2016).

21. Desai, L. V. & Sanford, M. S. Construction of Tetrahydrofurans by Pd^{II}/Pd^{IV}-Catalyzed Aminooxygenation of Alkenes. *Angew. Chem. Int. Ed.* **46**, 5737−5740 (2007).

22. Kalyani, D.; Sanford, M. S. Oxidatively Intercepting Heck Intermediates: Pd-Catalyzed 1,2- and 1,1-Arylhalogenation of Alkenes. *J. Am. Chem. Soc*. **130**, 2150−2151 (2008).

23. Kalyani, D., Satterfield, A. D. & Sanford, M. S. Palladium-catalyzed oxidative arylhalogenation of alkenes: synthetic scope and mechanistic insights. *J. Am. Chem. Soc.* **132**, 8419–8427 (2010).

24. Talbot, E. P. A., Fernandes, T. de A., McKenna, J. M. & Toste, F. D. Asymmetric Palladium-Catalyzed Directed Intermolecular Fluoroarylation of Styrenes. *J. Am. Chem. Soc*. **136**, 4101−4104 (2014).

25. Liu, Z., Wang, Y., Wang, Z., Zeng, T., Liu, P. & Engle, K. M. Catalytic Intermolecular Carboamination of Unactivated Alkenes via Directed Aminopalladation. *J. Am. Chem. Soc*. **139**, 11261−11270 (2017).

26. Terao, J. & Kambe, N. Cross-Coupling Reaction of Alkyl Halides with Grignard Reagents Catalyzed by Ni, Pd, or Cu Complexes with π-Carbon Ligand(s). *Acc. Chem. Res.* **41**, 1545–1554 (2008).

27. Chatani, N. Nickel-Catalyzed Functionalization Reactions Involving C−H Bond Activation via an Amidate-Promoted Strategy and Its Extension to the Activation of C−F, C−O, C−S, and C−CN Bonds. *Acc. Chem. Res*. 10.1021/acs.accounts.3c00493 (2023).

28. Aihara, Y. & Chatani, N. Nickel-Catalyzed Direct Alkylation of C-H Bonds in Benzamides and Acrylamides with Functionalized Alkyl Halides via Bidentate-Chelation Assistance. *J. Am. Chem. Soc*. **135**, 5308−5311 (2013).

29. Heberer, N., Hu, C.-H. & Mirica, L. M. In Comprehensive Coordination Chemistry III (eds Constable, E. C. et al.) 348–374 (Elsevier, 2021).

30. Camasso, N. M. & Sanford, M. S. Design, Synthesis, and Carbon-Heteroatom Coupling Reactions of Organometallic Nickel(IV) Complexes. *Science* **347**, 1218−1220 (2015).

31. Bour, J. R., Camasso, N. M. & Sanford, M. S. Oxidation of Ni(II) to Ni(IV) with Aryl Electrophiles Enables Ni-Mediated Aryl−CF_3 Coupling. *J. Am. Chem. Soc*. **137**, 8034−8037 (2015).

32. D'Accriscio, F., Borja, P., Saffon-Merceron, N., Fustier-Boutignon, M., Mézailles, N. & Nebra, N. C-H Bond Trifluoromethylation of Arenes Enabled by a Robust, High-Valent Nickel (IV) Complex, *Angew. Chem. Int. Ed*. **56**, 12898–12902 (2017).

33. Sahni, P., Gupta, R., Sharma, S. & Pal, A. K. The once-elusive Ni(IV) species is now a potent candidate for challenging organic transformations. *Coord. Chem. Rev.* **474**, 214849 (2023).

34. Jensen, K. H. & Sigman, M. S. Mechanistic Approaches to Palladium-catalyzed Alkene Difunctionalization Reactions. *Org. Biomol. Chem.* **6**, 4083–4088 (2008).

35. Li, Y., Wu, D., Cheng, H.-G. & Yin, G. Difunctionalization of Alkenes Involving Metal Migration。 *Angew. Chem. Int. Ed.* **59**, 7990–8003 (2020).

36. Lee, B. C., Liu, C.-F., Lin, L. Q. H., Yap, K. Z., Song, N., Ko, C. H. M., Chan, P. H. & Koh, M. J. N-Heterocyclic Carbenes as Privileged Ligands for Nickel-Catalysed Alkene Functionalisation. *Chem. Soc. Rev*. **52**, 2946 (2023).

37. Coombs, J. R. & Morken, J. P. Catalytic Enantioselective Functionalization of Unactivated Terminal Alkenes. *Angew. Chem. Int. Ed.* **55**, 2636–2649 (2016).

38. Zhang, J.-S., Liu, L., Chen, T. & Han, L.-B. Transition-Metal-Catalyzed Three-Component Difunctionalizations of Alkenes. *Chem. Asian J.* **13**, 2277–2291 (2018).

39. Derosa, J., Apolinar, O., Kang, T., Tran, V. T. & Engle, K. M. Recent Developments in Nickel–Catalyzed Intermolecular Dicarbofunctionalization of Alkenes. *Chem. Sci*. **11**, 4287–4296 (2020).

40. Dhungana, R. K., Kc, S., Basnet, P. & Giri, R. Transition Metal–Catalyzed Dicarbofunctionalization of Unactivated Olefins. *Chem. Rec*. **18**, 1314–1340 (2018).

41. Qi, X. & Diao, T. Nickel-Catalyzed Dicarbofunctionalization of Alkenes. *ACS Catal*. **10**, 8542–8556 (2020).

42. Luo, Y.-C., Xu, C. & Zhang, X. Nickel-Catalyzed Dicarbofunctionalization of Alkenes. *Chin. J. Chem*. **38**, 1371–1394 (2020).

43. Wickham, L. M. & Giri, R. Transition Metal (Ni, Cu, Pd)-Catalyzed Alkene Dicarbofunctionalization Reactions. *Acc. Chem. Res*. **54**, 3415–3437 (2021).

44. Cong, H. & Fu, G. C. Catalytic Enantioselective Cyclization/Cross-Coupling with AlkylElectrophiles. *J. Am. Chem. Soc.* **136**, 3788−3791 (2014).

45. Shrestha, B., Basnet, P., Dhungana, R. K., Kc, S., Thapa, S., Sears, J. M. & Giri, R. Ni-Catalyzed Regioselective 1,2- Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. *J. Am. Chem. Soc*. **139**, 10653−10656 (2017).

46. Derosa, J., Tran, V. T., Boulous, M. N., Chen, J. S. & K. M. Engle, Nickel-Catalyzed β, γ-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling. *J. Am. Chem. Soc*. **139**, 10657−10660 (2017).

47. Li, W., Boon, J. K. & Yu Zhao, Nickel-Catalyzed Difunctionalization of Allyl Moieties Using Organoboronic Acids and Halides with Divergent Regioselectivities. *Chem. Sci*. **9**, 600–607 (2018).

48. Yang, T., Chen, X., Rao, W. & Koh, M. J. Broadly Applicable Directed Catalytic Reductive Difunctionalization of Alkenyl Carbonyl Compounds. *Chem* **6**, 738–751 (2020).

49. Wang, S., Luo, C., Zhao, L., Zhao, J., Zhang, L., Zhu, B. & Wang, C. Regioselective Nickel-Catalyzed Dicarbofunctionalization of Unactivated Alkenes Enabled by Picolinamide Auxiliary, *Cell Rep. Phys. Sci*. **2**, 100574 (2021).

50. Kang, T., Kim, N., Cheng, P. T., Zhang, H., Foo, K. & Engle, K. M. Nickel-Catalyzed 1,2-Carboamination of Alkenyl Alcohols. *J. Am. Chem. Soc.* **143**, 13962−13970 (2021).

51. Xie, L., Wang, S., Zhang, L. et al. Directed Nickel-Catalyzed Regio- and Diastereoselective Arylamination of Unactivated Alkenes. *Nat Commun* **12**, 6280 (2021).

52. Wang, H., Liu, C. F., Martin, R. T., Gutierrez, O. & Koh, M. J. Directing-Group-Free Catalytic Dicarbofunctionalization of Unactivated Alkenes. *Nat. Chem.* **14**, 188–195 (2022).

53. Li, Z.-Q., Cao, Y., Kang, T. & Engle, K. M. Electrophilic Sulfur Reagent Design Enables Directed *syn*-Carbosulfenylation of Unactivated Alkenes. *J. Am. Chem. Soc*. **144**, 7189−7197 (2022).

54. Kang, T., González, J. M., Li, Z.-Q., Foo, K., Cheng, P. T. W. & Engle, K. M. Alkene Difunctionalization Directed by Free Amines: Diamine Synthesis via Nickel-Catalyzed 1,2-Carboamination. *ACS Catal.* **12**, 3890−3896 (2022).

55. Rao, C., Zhang, T., Liu, H. & Huang, H. Double Alkyl–Alkyl Bond Construction Across Alkenes Enabled by Nickel Electron-Shuttle Catalysis. *Nat. Catal.* **6**, 847–857 (2023).

56. Wu, D., Kong, W., Bao, Y. *et al*. Alkene 1,1-Difunctionalizations via Organometallic-Radical Relay. *Nat. Catal*. DOI: 10.1038/s41929-023-01032-0 (2023).

57. Wang, D.-M., She, L.-Q., Yuan, H., Wu, Y, Tang, Y. & Wang, P. Ligand-Enabled Ni^{II}-Catalyzed Hydroxylarylation of Alkenes with Molecular Oxygen. *Angew. Chem. Int. Ed*. **62**, e202304573 (2023).

58. Watson, M. B., Rath, N. P. & Mirica, L. M. Oxidative C−C bond formation reactivity of organometallic Ni(II), Ni(III), and Ni(IV) complexes. *J. Am. Chem. Soc*. **139**, 35−38 (2017).

59. Hu, C.-H., Kim, S.-T., Baik, M.-H. & Mirica, L. M. Nickel−Carbon Bond Oxygenation with Green Oxidants via High-Valent Nickel Specie. *J. Am. Chem. Soc*. **145**, 11161−11172 (2023).

60. Wang, D. M., She, L. Q., Wu, Y., Zhu, C. & Wang, P. Ligand-enabled Ni-Catalyzed Hydroarylation and Hydroalkenylation of Internal Alkenes with Organoborons. *Nat. Commun.* **13**, 6878 (2022).

61. Taylor, A. M., Côté, A. *et al*. Fragment-Based Discovery of a Selective and Cell-Active Benzodiazepinone CBP/EP300 Bromodomain Inhibitor (CPI-637). *ACS Med. Chem. Lett*. **7**, 531−536 (2016).

62. Nagarajan, S. R., Lu, H.-F. *et al*. Discovery of +(2-{4-[2-(5,6,7,8-Tetrahydro-1,8-Naphthyridin-2-yl)ethoxy]phenyl}-Cyclopropyl)Acetic Acid as Potent and Selective $\alpha_v\beta_3$ inhibitor: Design, Synthesis, and Optimization. *Bioorg. Med. Chem.* **15**, 3390–3412 (2007).

63. Alvarado, M. *et al*. Synthesis and Binding Affinity of Novel 3-Aminoethyl-1-tetralones, Potential Atypical Antipsychotics. *Bioorg. Med. Chem. Lett*. **15**, 3063–3066 (2005).

64. Diccianni, J. B. & Diao, T. Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions. *Trends Chem*. **1**, 830–844 (2019).

65. Hu, X. Nickel-Catalyzed Cross Coupling of Non-Activated Alkyl halides: A Mechanistic Perspective. *Chem. Sci*. **2**, 1867–1886 (2011).

66. Qin, T., Cornella, J., Li, C., Malins, L. R., Edwards, J. T., Kawamura, S., Maxwell, B. D., Eastgate, M. D. & Baran, P. S. A General Alkyl-Alkyl Cross-Coupling Enabled by Redox-Active Esters and Alkylzinc Reagents. *Science* **352**, 801–805 (2016).

67. Griller, D. & Ingold, K. U. Free-radical clocks. *Acc. Chem. Res.* **13**, 317–323 (1980).

Data Availability

All information relating to optimization studies, experimental procedures, mechanistic studies, NMR spectra, high-resolution mass spectrometry are available in the Supplementary Information. All other data are available from the corresponding authors upon request.

Supplementary Information is available in the online version of the paper.

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