Title:

Non-innocent electrophiles unlock exogenous base-free coupling reactions.

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Abstract:

Transition metal catalysis has revolutionized our ability to precisely manipulate matter and has placed itself at the forefront of the combat against societal challenges[1] through key discoveries in drug design[2], agriculture[3], material synthesis[4] and environmental sciences[5]. Numerous important transition metal catalyzed reactions rely on stoichiometric quantities of an exogenous base to enable catalytic turnover[6]. Despite playing a fundamental role, paradoxically, the base poses major challenges on several fronts, such as restricting the accessible chemical space due to functional group incompatibilities, or causing heterogeneous reaction mixtures that affect reproducibility, scale-up campaigns, and the implementation of emerging technologies, e.g. flow chemistry or high-throughput experimentation[7-16]. Ultimately, this impedes innovation across multiple areas. Here we introduce a unifying strategy that eliminates the need for an exogenous base through the use of non-innocent electrophiles (NIE). Key to its success was the encryption of the base into the electrophile rendering it non-innocent, thus preserving the synthetic utility of the original reaction while overcoming the challenges associated with the exogenous base. The use of nickel as an earth-abundant metal catalyst as well as the employment of ubiquitous phenol derivatives[17] as non-innocent electrophiles are further salient features of this sustainable protocol[18-20]. The universal applicability of this concept was demonstrated by turning multiple traditionally base-dependent catalytic reactions, e.g. the Buchwald-Hartwig amination, the Mizoroki-Heck reaction and the Suzuki-Miyaura coupling, into exogenous base-free homogeneous processes. In a broader context, the results presented in this work provide a conceptual blueprint for the utilization of non-innocent electrophiles to overcome core limitations and unlock novel features in catalysis.

Main Text:

The union of a base and a transition metal catalyst marked a paradigm shift in catalysis as it enabled the combination of readily available and benign precursors in a previously unthinkable manner. Prominent examples include the Buchwald-Hartwig amination (BHA), the Mizoroki-Heck reaction (MHR) as well as the Suzuki-Miyaura coupling (SMC), all of which have transcended their own field to become go-to tools for the discovery of important medicines, materials, and methods in both academia and industry[7,21-23].

Despite the outstanding achievements that such catalytic reactions have brought about, the requirement for a base represents one of their major drawbacks (Fig. 1a). First, from a synthetic standpoint, the accessible chemical space is restricted due to functional group (FG) incompatibilities resulting from the basic reaction conditions[7-12]. Second, the use of an exogenous base generates additional stoichiometric waste, often leading to tedious waste management that further diminishes the overall sustainability of a process[18-20], possibly creating a barrier to the adoption of an otherwise formidable synthetic route, especially on a larger scale. Finally, operational aspects including reproducibility[13] and scale-up[14], or the use of innovative technologies such as flow chemistry[15] or high-throughput experimentation[16], can be affected due to the resulting heterogeneity of the reaction mixture caused by the insoluble, inorganic bases that are commonly used.

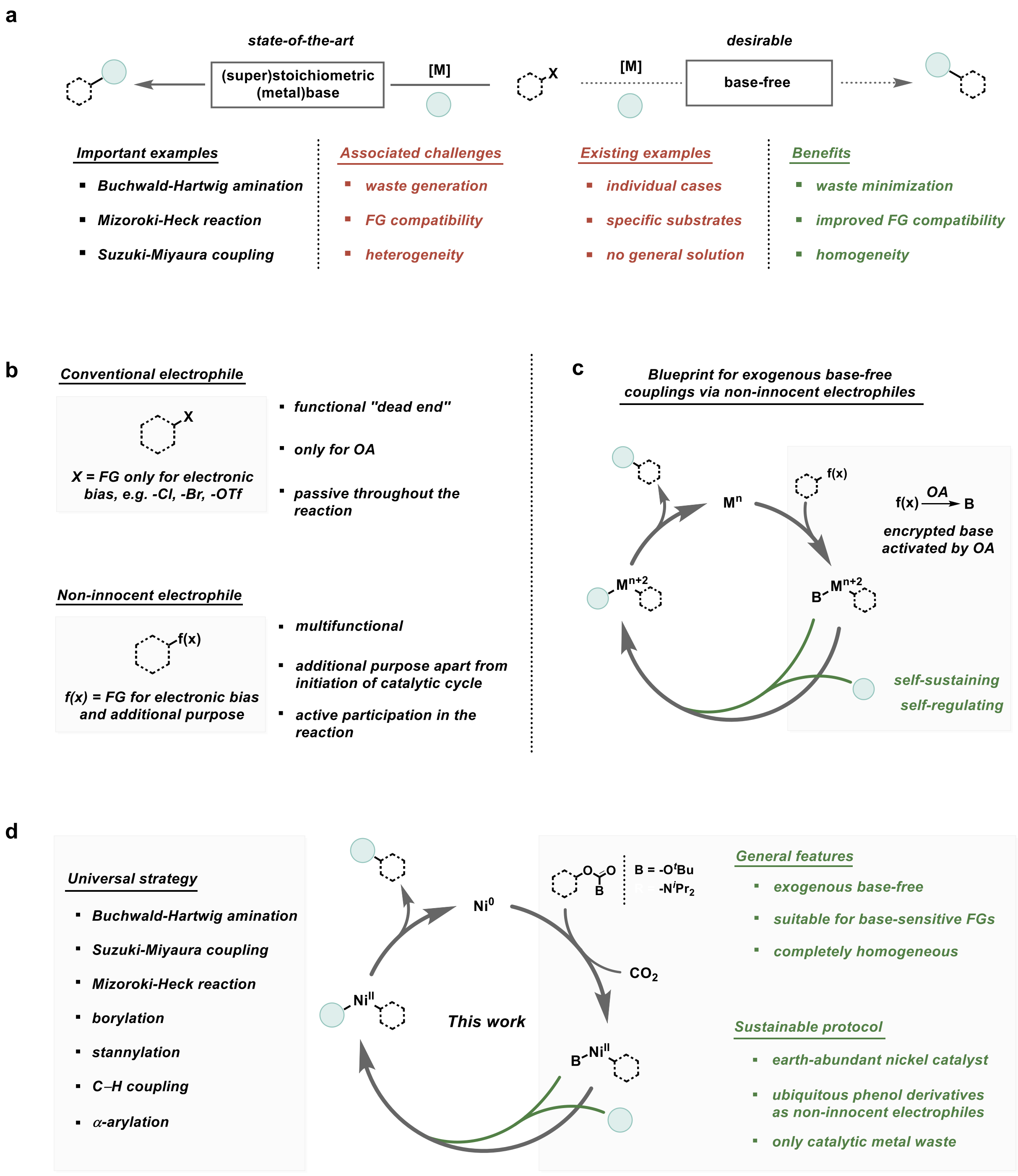


Fig. 1 Context of this work. **a**: State-of-the-art with important examples, associated challenges and the benefits of base-free processes. **b**: Comparison of conventional and non-innocent electrophiles. **c**: Blueprint for creating exogenous base-free coupling reactions via non-innocent electrophiles. **d**: Developed method based on a Ni catalyst and phenol derivatives as non-innocent electrophiles. FG = functional group; OA = oxidative addition; OTf = triflate; B = base.

Therefore, a general approach that eludes the need for an exogenous base would reduce the environmental impact while simultaneously expanding the utility of these reactions. Furthermore, the implementation of novel technologies that have so far suffered from base-related challenges would pave the way for innovative discoveries with potentially far-reaching consequences. However, due to the fundamental role of the base in coupling reactions, such base-free protocols are scarce, with isolated examples reported for coupling partners like diazonium salts[24,25] or fluorinated compounds[26], along with decarbonylative[27-29], directed[30,31] or intramolecular approaches[32]. Thus, there is currently no general solution to this long-standing challenge in catalysis.

We therefore questioned whether all these challenges could be addressed with a unified strategy, while simultaneously preserving the powerful synthetic abilities of the original reactions. Considering the fact that coupling reactions generally employ electrophiles to provide the electronic bias for the initiation of the catalytic cycle, we reasoned that this could serve as an ideal platform to establish such a concept. Inspired by pioneering examples of exogenous base-free allylic substitution reactions[33-35], we envisaged the use of multifunctional electrophiles, termed non-innocent electrophiles (NIE), which are equipped with an encrypted base that can be released upon oxidative addition (OA). As a consequence of this design, the base is concealed off-cycle but can be released in catalytic amounts by on-demand activation via OA, thus mitigating the traditional detrimental effects caused by an exposure of the substrates to high concentrations of base. Moreover, the omission of any exogenous base would render the reaction conditions completely homogeneous and establish a process which only generates catalytic amounts of metal waste (Fig. 1b and c).

Based on this design principle, we began our investigation by evaluating selected electrophiles (**1-5**) that display functional groups endowed with the possibility to release a base upon reaction with a transition metal (Fig. 2a). For that purpose, four prototypical conditions varying the coupling partner according to the corresponding reaction, i.e. aniline **6** for the BHA, styrene **7** for the MHR and boronic acid **8** for the SMC, were chosen for initial exploration. Our hypothesis was confirmed early on, as all three reactions generated, under certain reaction conditions, a significant amount of product in the absence of exogenous base, using either carbonate **3** or carbamate **4** as substrates (Fig. 2b). While seminal reports in the field of C−O bond activation have previously demonstrated that both substrate classes are competent coupling partners for the BHA[36-38], the MHR[39] as well as the SMC[40], to the best of our knowledge, exogenous base-free reaction conditions have never been developed. For the BHA and the MHR, carbamate **4** under conditions **III** afforded amine **9** and alkene **10** in promising initial yields of 54% and 36%, respectively. After assessment of different parameters, the more sterically hindered carbamate **12** was found to deliver superior results in comparison to carbamate **4** by preventing deleterious intramolecular amination[32]. Further, in the case of the BHA, a change of the ligand to 3,4-bis(dicyclohexylphosphaneyl)thiophene (dcypt) [41] led to a highly efficient process starting from equimolar amounts of carbamate **12** and aniline **6** yielding amine **9** almost quantitatively. Likewise, the MHR provided good results after slight adjustments affording alkene **10** in 73% yield. Regarding the SMC, carbonate **3** displayed remarkable activity under conditions **II** affording biaryl **11** in 88% yield (Fig. 2c).

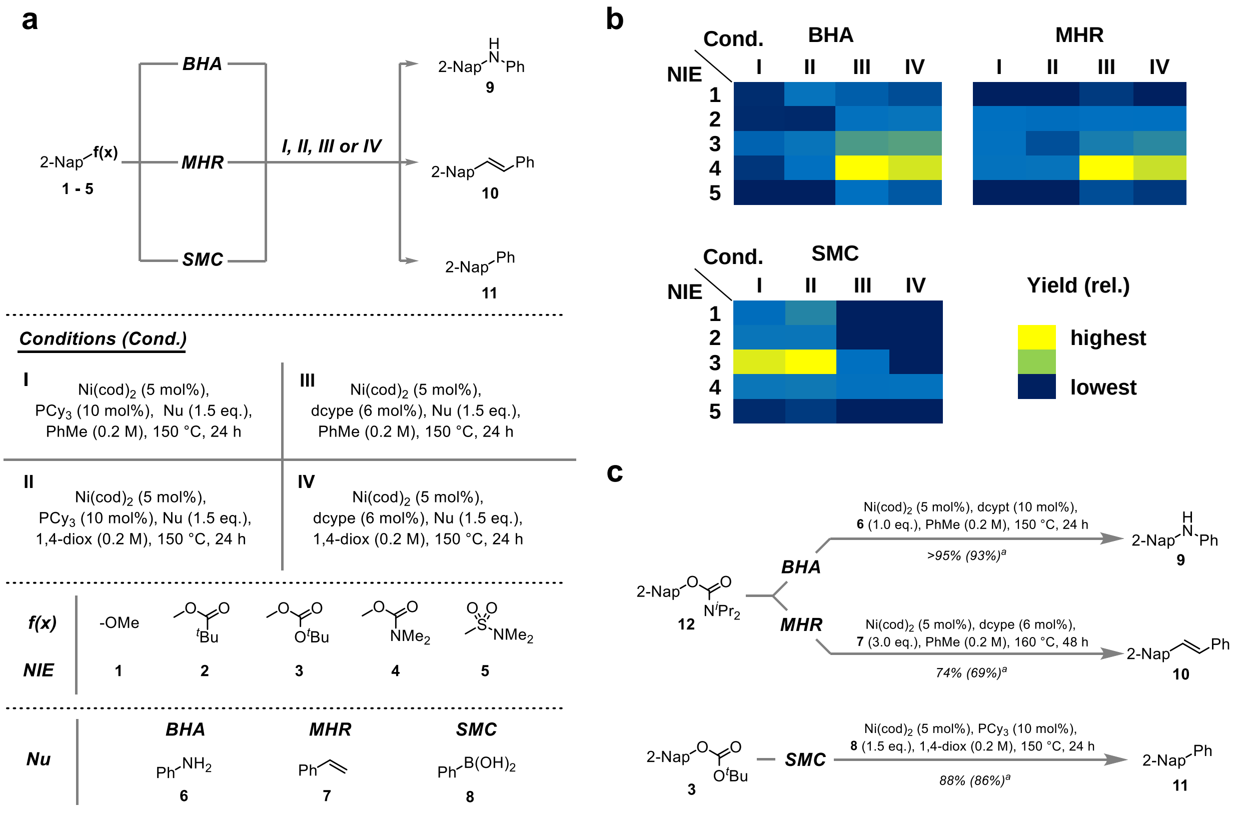


Fig. 2 Reactivity assessment and optimized conditions. a: Reactivity assessment with conditions, NIE and Nu. **b**: Initial hit results with relative yields. **c**: Optimized conditions for the BHA, MHR and SMC. ^{a}GC yield (isolated yield in parentheses). Ph = phenyl; Me = methyl; ^{t}Bu = *tert*-butyl; ^{i}Pr = *iso*-propyl; 2-Nap = 2-naphthalenyl; cod = 1,5-cyclooctadiene; Cy = cyclohexyl; dcype = 1,2-bis(dicyclohexylphosphaneyl)ethane; dcypt = 3,4-bis(dicyclohexylphosphaneyl)thiophene; PhMe = toluene; diox = dioxane; eq. = equivalent(s); NIE = non-innocent electrophile; Nu = nucleophile; rel. = relative; BHA = Buchwald-Hartwig amination; MHR = Mizoroki-Heck reaction; SMC = Suzuki-Miyaura coupling.

With the optimized conditions in hand, the substrate scope was investigated. Given the unprecedented nature of a base-free intermolecular BHA with a general application profile, we selected this important C−N bond forming reaction to showcase the broad potential of NIEs (Fig. 3).

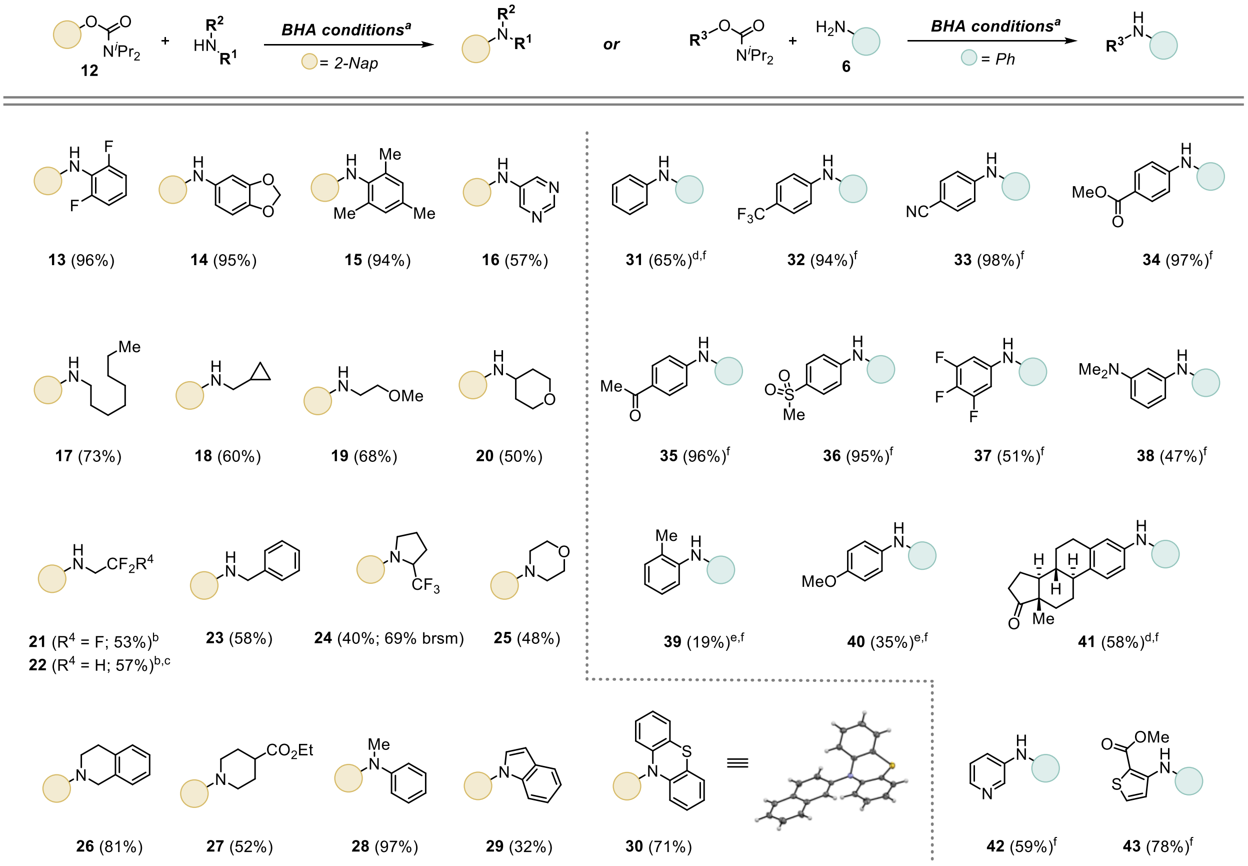
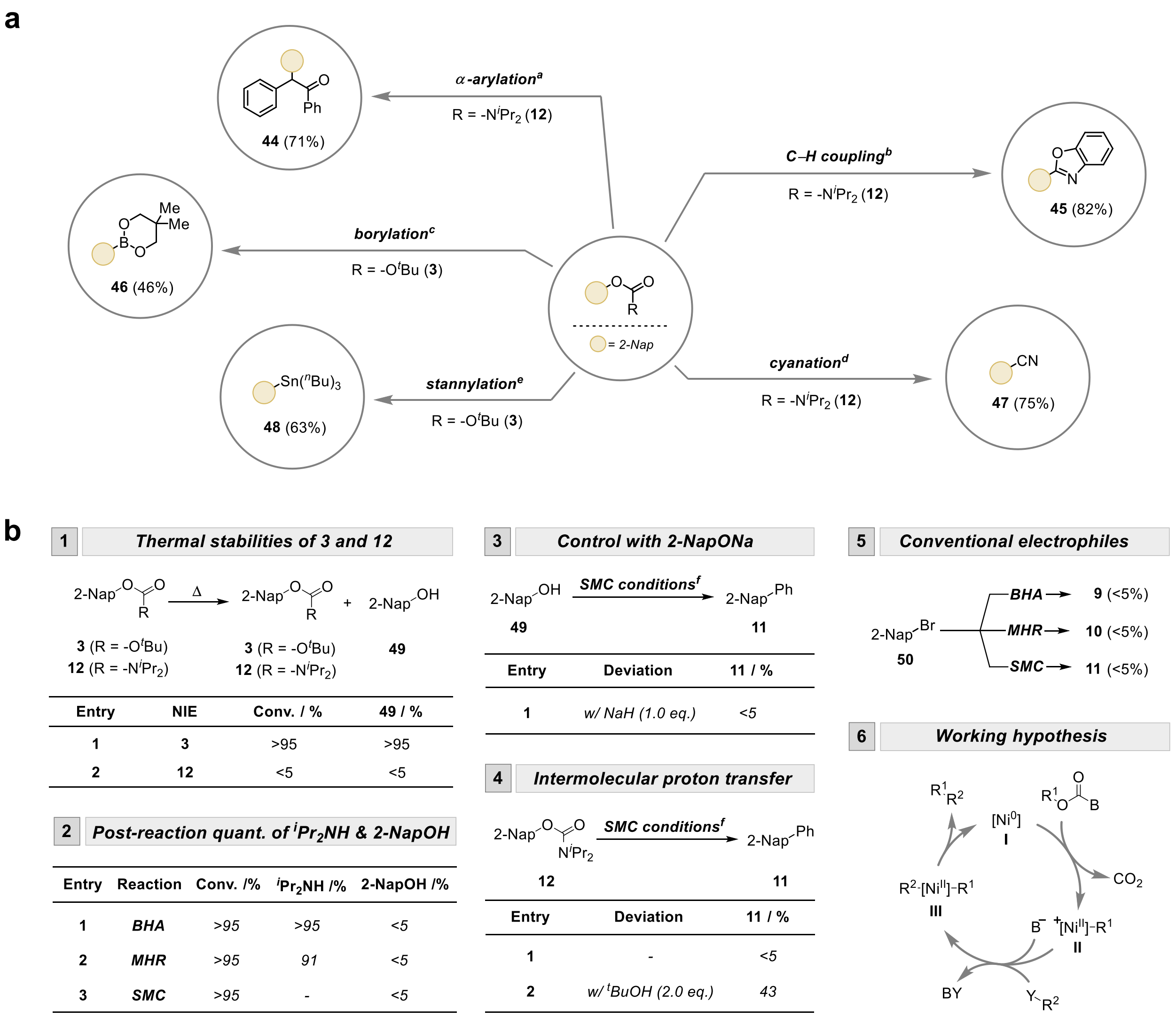


Fig. 3 Scope of the exogenous base-free Buchwald-Hartwig amination. Isolated yields in parentheses; ^{a}Ni(cod)$_2$ (5 mol%), dcypt (10 mol%), NIE (1.0 eq.), amine (1.0 eq.), PhMe (0.2 M), 150 °C, 24 h; ^{b}2.0 eq. amine used; ^{c}isolated as the HCl salt; ^{d}Ni(cod)$_2$ (10 mol%), dcypt (20 mol%), NIE (1.5 eq.), amine (1.0 eq.), PhMe (0.2 M), 160 °C, 24 h; ^{e}Ni(cod)$_2$ (10 mol%), dcypt (20 mol%), NIE (2.0 eq.), amine (1.0 eq.), PhMe (0.2 M), 160 °C, 24 h; ^{f} <5% yield w/o Ni(cod)$_2$; 2-Nap = 2-naphthalenyl; cod = 1,5-cyclooctadiene; dcypt = 3,4-bis(dicyclohexylphosphaneyl)thiophene; ^{i}Pr = *iso*-propyl; Me = methyl; Et = ethyl; brsm = based on recovered starting material; PhMe = toluene; w/o = without; eq. = equivalent(s); BHA = Buchwald-Hartwig amination; NIE = non-innocent electrophile.

A diverse set of primary as well as secondary aryl-/alkylamines could be employed. Aryl amines displayed excellent performance allowing for near quantitative coupling throughout most of the substrate scope (**13-15**, **28**). Notably, base-sensitive primary as well as secondary β-fluorinated alkylamines^8 led to satisfactory yields of the corresponding products (**21, 22, 24**). Regarding the scope of the electrophilic coupling partner, a diverse range of diisopropyl aryl carbamates were readily prepared and exposed to the reaction conditions using aniline **6** as the coupling partner. Electron-deficient substrates (**32-36**) afforded the products in almost quantitative yields, whereas electron-rich ones (**31**, **39-41**) required slight adjustments of the reaction conditions to provide satisfactory results. Furthermore, various functional groups were compatible including electrophilic ones such as nitriles (**33**), esters (**34, 43**) and ketones (**35, 41**). Notably, the polyfluorinated amine **37** could be isolated in moderate yield despite the potential for oxidative addition into the C−F bond by the nickel catalyst[42]. Moreover, estrone derived amine **41** could be readily accessed. Importantly, 6-membered- as well as 5-membered heteroaromatic carbamates could be transformed into the corresponding amines **42** and **43** in good yields. In summary, the scope investigation highlighted the fact that the regulatory release mechanism of the encrypted base offered the anticipated benefits across a range of base-sensitive moieties on both coupling partners. Furthermore, control reactions with several different substrates demonstrated that the nickel catalyst is essential for the reaction as no significant product formation, i.e. <5% yield, could be observed in its absence (Fig. 3).

By having successfully applied the strategy to three important catalytic reactions, we were able to establish completely homogeneous processes which generate only catalytic amounts of metal waste as well as non-halogenated, easily removable stoichiometric by-products such as CO_2, *tert*-butanol or diisopropylamine.

We next shifted our attention towards expanding NIEs to other reactions (Fig. 4a).



Entry	NIE	Conv. / %	49 / %
1	3	>95	>95
2	12	<5	<5

Entry	Reaction	Conv. /%	^{i}Pr$_2$NH /%	2-NapOH /%
1	*BHA*	*>95*	*>95*	*<5*
2	*MHR*	*>95*	*91*	*<5*
3	*SMC*	*>95*	*-*	*<5*

Entry	Deviation	11 / %
1	*w/ NaH (1.0 eq.)*	*<5*

Entry	Deviation	11 / %
1	-	<5
2	*w/ ^{t}BuOH (2.0 eq.)*	*43*

Fig. 4 Extension of reactivity, working hypothesis and preliminary mechanistic experiments. a: NIEs in other reactions; ^{a}Ni(cod)$_2$ (5 mol%), dcypt (10 mol%), **12** (1.0 eq.), ketone (3.0 eq.), 1,4-diox (0.2 M), 160 °C, 24 h; ^{b}Ni(cod)$_2$ (5 mol%), dcypt (10 mol%), **12** (1.0 eq.), azole (3.0 eq.), 1,4-diox (0.2 M), 160 °C, 24 h; ^{c}Ni(cod)$_2$ (5 mol%), PCy$_3$ (10 mol%), **3** (1.0 eq.), B$_2$nep$_2$ (3.0 eq.), 1,4-diox (0.2 M), 150 °C, 24 h; ^{d}Ni(cod)$_2$ (5 mol%), dcype (10 mol%), **12** (1.0 eq.), 2-(dimethylamino)acetonitrile (1.5 eq.), 1,4-diox (0.2 M), 150 °C, 24 h; ^{e}Ni(cod)$_2$ (5 mol%), dcype (10 mol%), **3** (1.0 eq.), TMS-Sn(^{n}Bu)$_3$ (1.5 eq.), PhMe (0.2 M), 150 °C, 24 h; **b**: Working hypothesis and preliminary mechanistic experiments. ^{f}Ni(cod)$_2$ (5 mol%), PCy$_3$ (10 mol%), **12** *or* **49** (1.0 eq.), **8** (1.5 eq.), 1,4-diox (0.2 M), 150 °C, 24 h. 2-Nap = 2-naphthalenyl; cod = 1,5-cyclooctadiene; Cy = cyclohexyl; ^{i}Pr = *iso*-propyl; ^{t}Bu = *tert*-butyl; ^{n}Bu = *n*-butyl; Me = methyl; Ph = phenyl; dcype = 1,2-bis(dicyclohexylphosphaneyl)ethane; nep = neopentyl glycolato; dcypt = 3,4-bis(dicyclohexylphosphaneyl)thiophene; TMS = trimethylsilyl; PhMe = toluene; diox = dioxane; conv. = conversion; quant. = quantification; w/ = with; eq. = equivalent(s); B = base; NIE = non-innocent electrophile; BHA = Buchwald-Hartwig amination; MHR = Mizoroki-Heck reaction; SMC = Suzuki-Miyaura coupling.

Notably, the direct α-arylation of ketones (**44**) as well as the C−H coupling with azoles (**45**) proved feasible. Both results represent significant advancements to the field of sustainable catalysis as the intentional design resulted in a simple process connecting two minimally prefunctionalized substrates in a catalytic manner[18-20]. Furthermore, direct umpolung of the electrophilic carbon could be performed by turning carbonate **3** into boronate **46** and stannane **48**, two useful moieties with a diverse application profile. Finally, the installation of a CN group (**47**) was possible, unlocking versatile downstream functionalizations. Altogether, this investigation clearly demonstrates the broad applicability of this concept and provides lead results for diverse transformations (Fig. 4a). Importantly, similar transformations in the field of C−O bond activation were previously reported in the presence of an exogenous base[41,43-46].

Next, a preliminary mechanistic investigation was conducted to support our working hypothesis (Fig. 4b). Analysis of the thermal stabilities of NIEs **3** and **12** revealed that carbamate **12** was stable, in contrast to carbonate **3** which fully converted to 2-naphthol **49** (Fig. 4b 1). Interestingly, post-reaction analysis of the model SMC showed full consumption of carbonate **3**, yet, no significant amount of 2-naphthol **49** could be detected (Fig. 4b 2, Entry 3). To exclude any participation of an *in-situ* formed naphtholate[47], a control reaction was undertaken by subjecting 2-naphthol **49** and NaH to the SMC conditions, however, no product formation could be observed (Fig. 4b 3). Based on these results, an alternative pathway via thermal decarboxylation appears unlikely. Post-reaction analysis of the model BHA and MHR further revealed that the formation of diisopropylamine correspond to the conversion of carbamate **12** (Fig. 4b 2, Entries 1 & 2). In order to probe the base release mechanism, carbamate **12** was reacted with boronic acid **8**. In agreement with the initial results using carbamate **4**, no significant product formation could be observed (Fig. 4b 4, Entry 1). Nevertheless, addition of *tert*-butanol had a dramatic effect, enabling the reaction to deliver biaryl **11** in 43% (Fig. 4b 4, Entry 2). This observation is noteworthy, as it indicates that the reactivity can be externally modulated via an intermolecular proton transfer step, thus providing an additional control element. In line with previous reports[32] and the steric demand of diisopropylamide as well as *tert*-butanol, an outer-sphere mechanism via nickel species **II** could offer a plausible explanation (Fig. 4b 6). Lastly, conventional bromonaphthalene **50** failed to yield any product, further highlighting the unique reactivity of non-innocent electrophiles (Fig. 4b 5).

In a broader context, we believe that our results underline the benefits and potentials of non-innocent electrophiles and tear down a conceptual barrier providing promising new avenues for catalysis.

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Data availability

The data that support the findings of this study are available within the article and its Supplementary Information. Crystallographic data for compounds **22** and **30** were deposited on the Cambridge Structural Database and are freely available via the Cambridge Crystallographic Data Centre under CCDC numbers 2070177 and 2070176.

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Author contributions

G.T. conceived the project. G.T. designed and performed the experimental studies. B.M. supervised the research. Both authors contributed to the writing and editing of the final manuscript.

Competing interests

The authors declare no competing interests.

Materials & Correspondence

Correspondence and requests for materials should be addressed to B.M.