Nickel-catalyzed Suzuki–Miyaura cross-couplings of aldehydes

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Transition-metal-catalyzed cross-couplings have been extensively used in the pharmaceutical and agrochemical industries for the construction of diverse C–C bonds. Conventional cross-coupling reactions require reactive electrophilic coupling partners, such as organohalides or sulfonates, which are not environmentally friendly and not naturally abundant. Another disadvantage associated with these transformations is the need for an exogenous base to facilitate the key transmetalation step, and this reagent inevitably induces side reactions and limits the substrate scope. Here, we report an unconventional Suzuki-type approach to the synthesis of biaryls, through nickel-catalyzed deformylative cross coupling of aldehydes with organoboron reagents under base-free conditions. The transformation tolerates structurally diverse (hetero)aryl substituents on both coupling partners and shows high reactivity and excellent functional group tolerance. Furthermore, the protocol was carried out on gram scale and successfully applied to the functionalization of complex biologically active molecules. Mechanistic investigations support a catalytic cycle involving the oxidative addition of the nickel into the aldehyde C(acyl)–H bond with subsequent hydride transfer, transmetalation, decarbonylation and reductive elimination processes.

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The development of efficient methods for the selective construction of C-C bonds is of great significance because carbon skeletons exist in numerous biologically active molecules, pharmaceuticals, and functional materials. Since the 1970s, transition-metal-catalyzed cross-coupling reactions have attracted increasing attention, and they have become indispensable tools in the organic chemist’s arsenal. Although the cross coupling of aryl halides and sulfonates with a variety of organometallic or main-group reagents has been successfully applied in synthetic transformations, the generation of corrosive halogen and sulfur containing waste is detrimental from synthetic, as well as environmental perspectives. With the rapid development of organometallic chemistry, impressive progress has recently been achieved in the use of C–O, C–N and carbonyl electrophiles as attractive alternative coupling partners (Fig. 1a, left). However, challenges still exist with these electrophiles, limiting the scope and applicability of their reactions. For instance, protocols using C–O electrophiles are often hampered by the “naphthalene problem” in which only π-extended aromatic frameworks show high reactivity. Couplings of aromatic carbonylic acids to build bialyl species via decarbonylative pathways are restricted to electron-withdrawing group-containing substrates or a strong oxidant is required; the synthesis of bialyl species via the decarbonylative reaction of esters and amides is limited to specific substrates (phenyl esters and twisted amides) that require an additional step to be synthesized from carboxylic acids; and the use of an exogenous base may also limit the scope of reagents and substrates.

Based on the considerations mentioned above, an ideal synthetic approach to construct C–C bonds would be to use cross-coupling partners that are inexpensive, nontoxic, and readily available under conditions that are highly tolerant of diverse functional groups and are base free. Recently, the utilization of aldehydes as coupling partners has attracted growing interest in both academic and pharmaceutical laboratories. Prompted by the synthetic relevance of bialyl compounds, which are ubiquitous in the skeletons of pharmaceuticals and organic materials, we questioned whether it would be possible to build bialyl units through a formal deformativative pathway using aldehyde precursors. To date and to the best of our knowledge, a general synthesis of bialyl species via the C–C cross-couplings of aldehydes with organometallic reagents is unknown.

As part of our interest in developing viable protocols for the activation of inert chemical bonds using transition-metal catalysis, we herein report the nickel-catalyzed Suzuki–Miyaura cross coupling of aldehydes with organoboron compounds under base-free conditions (Fig. 1a, right). The catalytic C–C bond formation proceeds smoothly with various aromatic and heteroaromatic aldehydes, providing a useful synthetic strategy that uses aldehydes as unconventional electrophilic coupling partners in cross-coupling reactions that will inspire further exploration.

Results

Rational design. A description of our mechanistic concept is outlined in Fig. 1b and shows the challenges that must be addressed to develop the nickel-catalyzed bialyl coupling of aldehydes. Our initial efforts sought to identify conditions that avoid the undesired decarbonylation (I to II) of the acynickel(II) hydride species that arises from the oxidative addition of the C(acyl)-H bond of the aldehyde to L\(_2\)Ni(0)20,21. Arylnickel(II) hydride II preferentially undergoes very fast reductive elimination (II to III) rather than transmetalation (II to V). Thus, to avoid the undesired reductive coupling and formation of arene III22, we envisioned that a key hydride abstraction or transfer from the acynickel(II) hydride to a suitable H-acceptor would enable the transmetalation (I to IV) while suppressing the decarbonylation-reductive coupling pathway. The subsequent aryl migration (IV to V) and reductive elimination would provide the cross-coupling product and regenerate the Ni catalyst. Based on these considerations, the ideal H-acceptor needs to (i) be perfectly compatible; (ii) be readily available; and (iii) have dual functionality in that it can both suppress reductive coupling through hydride abstraction and simultaneously promote transmetalation to allow base-free conditions (Fig. 1c). Therefore, ketones were considered as possible H-acceptors because they would suit all of these requirements (they are readily available, stable, compatible, and good H-acceptors for the hydride-transfer step, and the formed alcoholate is a good activator for the transmetalation of the boronate). This hypothesis was corroborated by DFT studies (Fig. 1c), which accompanied the experimental study and provided the base-free cross coupling of aldehydes with organoboron compounds under nickel catalysis.

Fig. 1 Nickel-catalyzed deformativative Suzuki–Miyaura cross coupling and related DFT studies on the role of trifluoroacetophenone. a Previously reported transition-metal-catalyzed construction of bialyl motifs (left) and nickel-catalyzed deformativative cross coupling for the synthesis of bialyls (right). b Proposed mechanism for the nickel-catalyzed arylation of aldehydes. c Dual-role of the ketone in the hydride-transfer and transmetalation steps.
revealed that the energy barriers for hydride transfer and base-free transmetalation were significantly decreased (23.0 and 26.7 kcal/mol, respectively) by the presence of trifluoroacetonophene, while the same decreases were not seen with other acceptors, such as benzophenone and acetonophene.

**Optimization of the reaction conditions.** Based on our mechanistic design, we began our primary investigations. Nicotinaldehyde (1a) and phenylboronic acid neopentylglycol ester (2a) were chosen as coupling partners in the presence of a nickel/ligand catalytic system with the use of a ketone as a hydride acceptor. After systematically evaluating the reaction parameters, we found that a combination of Ni(cod)2 and trioctylphosphine (P(Oct)3) afforded the biaryl product in 77% yield under base-free conditions when trifluoroacetonophene (4a) was employed as the hydride acceptor. Control experiments revealed that each reagent, namely, the catalyst, ligand and hydride acceptor, were all critical for the success of this reaction (Fig. 2a). Attempts under relatively lower temperature (130 °C) gave moderate yield. To date, reactions with other organoborane reagents have been less productive (see Supplementary Table 1). Regarding the influence of the ligand, replacement of trioctylphosphine with tri-n-propylphosphine (PnPr3) or tri-n-butylphosphine (PnBu3) under identical reaction conditions slightly decreased the yield, while the use of a bidentate phosphine ligand (dicyclopentadienylmethylphosphine (H/Cp2)) or N-heterocyclic carbene ligand IPrHCl gave unsatisfactory results (Fig. 2b). To facilitate the key hydride-transfer process, we evaluated several ketones (4a–e). However, for the reasons described, trifluoroacetonophene (4a) was the most effective hydride acceptor (Fig. 2c). Furthermore, commercially available and air-stable nickel precatalyst, Ni(OAc)2·4H2O can be applied but results in lower yields (see Supplementary Table 3).

**Substrate scope.** Encouraged by the initial results, we examined the scope of the reaction with respect to various aromatic and heteroaromatic boronic ester nucleophiles in combination with nicotinaldehyde (1a) as the coupling partner. As shown in Fig. 3, we found that with our catalytic system, various phenyl boronic ester substrates, bearing either electron-donating or electron-withdrawing functional groups, could be converted into the corresponding biaryl products in good yields. The use of methyl-substituted or tert-butyl-substituted phenylboronic esters smoothly provided the corresponding products (3Ab–3Ad), whereas the use of biphenyl boronic ester gave 3Ac in 64% yield. Furthermore, not only naphthyl-derived substrates (3Af, 3Ag) but also phenyl boronic ester derivatives possessing ethoxy (3Aj), silyl (3Ak), amine (3Al), fluoro (3Am–3Ao), trifluoromethyl (3Ap, 3Aq), trifluoromethoxy (3Ar), cyano (3As), ester (3At), and amide (3Au) substituents are perfectly suitable for the transformation and gave the desired products in good yields. Importantly, our decarbonylative cross-coupling reaction could be readily extended to heteroaromatic boronic esters derived from (benzo)furans and (benzo)thiophene, affording the corresponding biheteroaryl motifs 3Av–3Aa. In addition, the two examples of estrone and δ-tocopheryl derivatives (3Abb and 3Ace) highlight the applicability of this method for the late-stage modification of complex molecules. We subsequently turned our attention to a series of aldehydes as electrophilic coupling partners to determine the scope of our method. Figure 3 also shows the excellent chemoselectivity profile of the developed method; phenyl, naphthyl, phenanthryl and fluorenyl aldehydes were suitable for this transformation (3Ba–3Fa). Although nickel catalysts have been successfully used for arylation reactions with boronic ester nucleophiles through C–OMe11 or C–F2 cleavage, we found that, in our case, these cleavage reactions did not compete with the deformylative biaryl synthesis (3Ha–3Ka and 3Na). This chemoselectivity is a general requirement for an applicable reaction and is also important for retrosynthesis planning. In addition, the chemoselectivity of this method was nicely illustrated by the fact that functional groups such as dioxole (3La), trifluoromethyl (3Oa and 3Pa), trifluoromethoxy (3Qa), and ester (3Ra) were well tolerated under the present conditions. It was further demonstrated that pyridine-derived, benzofuran-derived, benzothiophene-derived, quinoline-derived, and furan-derived heterocyclic aldehydes (3Sa–3Wa) did not hinder the success of the transformation. Regarding the mentioned chemoselectivity, bioactive natural product compounds such as menthol, galactose, cholesterol and pregnenolone were also suitable substrates for this reaction, effectively providing the desired products 3Xa–3Aa.

**Mechanistic studies.** We conducted several experiments to elucidate the reaction mechanism. We first performed an isotopelabeling experiment with a deuterated benzaldehyde. The deuterium of [D1]-1b was shown to add to the carbonyl group of the hydrogen acceptor (trifluoroacetonophene, 4a) to give [D1]–2,2,2-trifluoro-1-phenylethan-1-ol (5) upon hydrolysis, which provides direct evidence for the occurrence of a hydride-transfer process during the cross-coupling reaction (Fig. 4a). To determine whether this hydride-transfer step is the rate-determining step of this cross-coupling process, we carried out a KIE (kinetic isotope effect) experiment. A minor kinetic isotope effect (kH/kD = 1.2) was found when using isotopically labeled aldehyde substrate [D1]-1b. This observation indicates the C(acyl)-H insertions and hydride-transfer processes are relatively fast (Fig. 4b).

Furthermore, we performed detailed DFT calculations (Fig. 4 and Supplementary Discussion) to rationalize and support our proposed mechanism for the nickel-catalyzed arylation of aldehydes. As a model system, we investigated the reaction of aldehyde 1b with phenylboronic ester 2a in the presence of Ni0 (PnPr3)2 (A) as the active catalyst. The reaction starts with the oxidative addition of aldehyde 1b to the active catalyst, Ni0 (PnPr3)2 (A), which proceeds via adduct B and transition state
Next, in the presence of aryl boronic ester (0.4 mmol, 2.0 equiv.), Ni(cod)2 (0.02 mmol, 10 mol%), P(Oct)3 (0.04 mmol, 20 mol%), and dioxane (1.5 ml) at 160 °C for 36 h. Yields after isolation.

In the next step, resulting (acyl)NiII-21.4 kcal/mol, while the barrier for C(aryl)-C(acyl) activation is 26.7 kcal/mol. Notably, compound 4a not only acts as an H-acceptor but also facilitates the transmetalation step to allow the cross-coupling to proceed in the absence of a base.

**Discussion**

In summary, we have developed a nickel-catalyzed decarbonylative arylation reaction of aldehydes with boronic esters. In contrast to classical cross-coupling reactions, this protocol...
allows the use of inexpensive, nontoxic, and readily available aldehydes as unconventional coupling electrophiles. The high reactivity, broad substrate scope, and scalability of this method suggest that this protocol can be a powerful alternative to the existing methodologies for the synthesis of structurally diverse biaryls. Importantly, our developed protocol shows high chemoselectivity, and functional groups, including C–Ome, C–F, and C–CO2R, which can be reactive in nickel-catalyzed functional group interconversions, are preserved. Moreover, mechanistic studies based on control experiments and DFT calculations revealed that the formation of biaryl products follows a reaction pathway that includes the oxidative addition of the (acetyl)-H bond of aldehyde to a Ni species with subsequent hydrogen transfer, transmetalation, aryl migration, and reductive elimination. Based on the described strategy further C–C and C–heteroatom bond forming reactions of aldehydes are expected.

**Methods**

**General procedure for the deformylative coupling.** In a nitrogen-filled glovebox, a 10-mL oven-dried sealed tube containing a stirring bar was charged with the corresponding aldehyde 1 (0.20 mmol, 1.0 equiv.), aryl/heteroaryl boronic ester 2 (0.40 mmol, 2.0 equiv.) and yellow Ni(cod)2 (5.5 mg, 10 mol%). Subsequently, HPLC grade 1,4-dioxane (1.5 mL) was added, and then trioctylphosphine ligand (18 μL, 20 mol%), and 2,2,2-trifluoroacetophenone (42 μL, 0.30 mmol, 1.5 equiv.) were added, respectively, via microsyringe. The tube with the mixture was sealed and removed from the glovebox. After stirring at 160 °C for 36 h, the mixture was allowed to cool to room temperature, diluted with EtOAc (5 mL) and filtered through a celite plug, eluting with additional EtOAc (15 mL). The filtrate was concentrated and purified by column chromatography on silica gel to yield the title product.

**Computational details.** All the geometries were optimized with the generalized gradient approximation (GGA) method with Gaussian 09, Revision D.0125 using the long-range-corrected hybrid DFT functional wB97x-D26. The electronic configuration of all the non-metal elements was described with the Ahlrichs split-valence polarization basis function Def2-SVP while Ni is treated with the triple-ζ valence basis set Def2-TZVP. The geometries were optimized without any symmetry constraints. Harmonic force constants were computed at the optimized geometries to characterize the stationary points as minima or saddle points. All transition states were optimized using the default Berry algorithm implemented in the Gaussian09 code25. For transition state structures, IRC calculations were undertaken to confirm the transition states which were connected to the correct minima. For further validation of energetics, single-point calculations were performed on the wB97x-D/Def2-TZVP(Ni)/Def2-SVP (non-metal) level optimized geometries using meta-hybrid-GGA functional M06 employing a valence triple-ζ type of basis set Def2-TZVP27,28 for all atoms. The solvent effects (1,4-dioxane, ε = 2.2099) were evaluated implicitly by a self-consistent reaction field (SCRF) approach for all the intermediates and transitions states, using the SMD continuum solvation model29. Unless specified otherwise, the ΔG value was obtained by augmenting the Eel energy terms at M06 (SMD)/Def2-TZVP with the respective free energy corrections at the wB97x-D/Def2-TZVP (Ni)/Def2-SVP (non-metal) level in gas phase. In all cases, the default integral grid (Fine Grid) was employed. The simplified trialkyl-phosphine ligand...
DFT calculations are available with the submitted manuscript.

Data availability

PnPr3 was used in the DFT calculation, which gave 53% yield (see Supplementary Table 1, entry 4).

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Author contributions

L.G. discovered the catalytic reactions. L.G., W.S., C.Z., L.C., and M.R. designed the experiments and analyzed the data. L.G., W.S., and X.L. performed the theoretical calculations. M.R. directed and supported the research. L.G., C.Z., and M.R. wrote the manuscript.

Additional information

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