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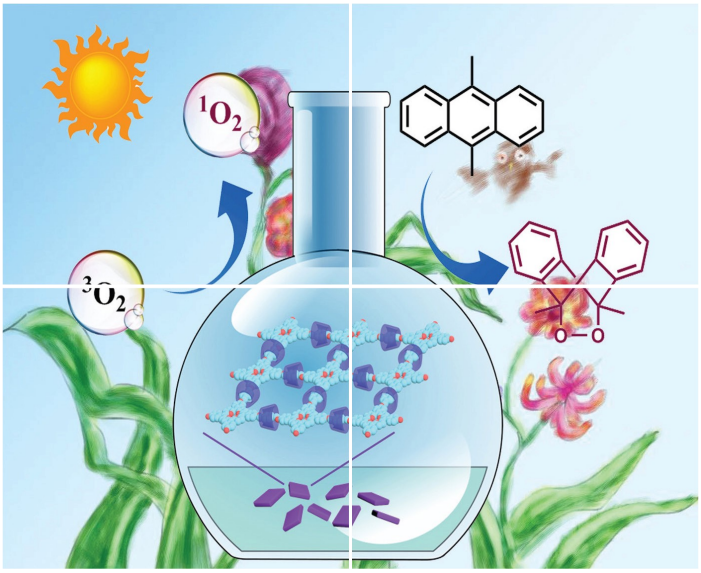

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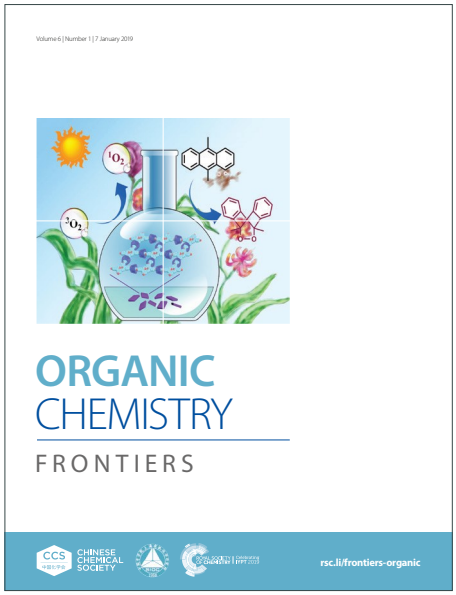

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ARTICLE

Reductive coupling of aryl (pseudo)halides towards symmetrical biaryls via a dual Ni/photoredox catalysis

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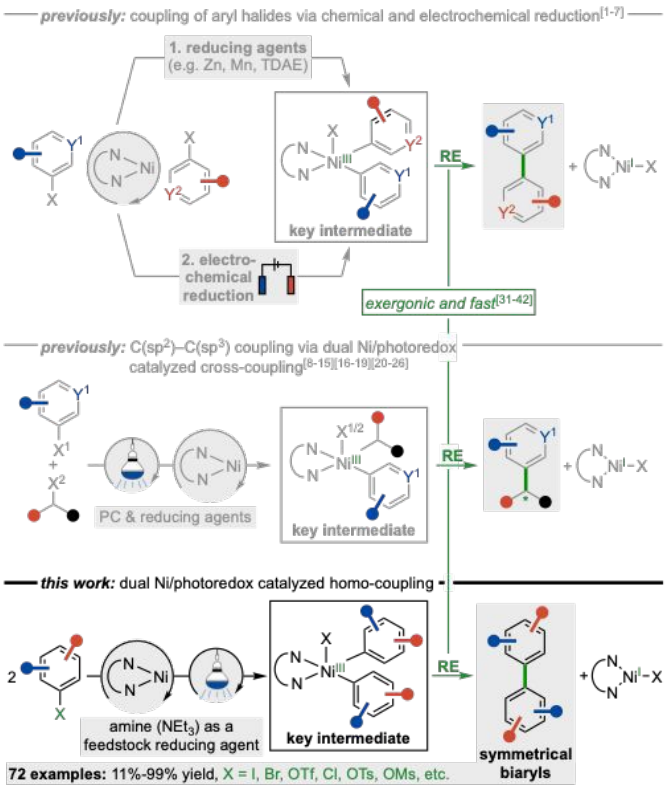
We demonstrate that dual Ni/photoredox catalysis enables a general reductive approach to symmetrical biaryls using simple amines as mild reducing agents. Guided by mechanistic considerations and DFT studies, NEt_3 was identified as an inexpensive and effective reductant for the homocoupling of readily accessible aryl (pseudo)halides. This strategy provides access to a wide range of highly functionalized biaryls in generally high yields under mild conditions. The synthetic utility of the method is demonstrated by the preparation of structurally diverse compounds, including the hepatitis C drug daclatasvir.

Introduction

In the recent past, reductive C–C coupling reactions have emerged as a powerful alternative to traditional, predominantly Pd-catalyzed cross-coupling reactions employing an organometallic nucleophile R–M (M = B, Zn, Mg, Sn, etc.) and an electrophile R–X (e. g. (pseudo)halides). Utilizing stable and widely available (pseudo)halide electrophiles and earth-abundant, non-precious metal-based catalysts three modes of reduction for these reductive coupling reactions have been developed to date: 1. reduction via the stoichiometric application of strong reducing agents, such as Zn, Mn or TDAE; 2. reduction employing electrochemical set-ups, which often allow for the avoidance of reducing reagents; 3. photoredox catalysis providing the necessary redox potentials for the application of weak and abundant reducing agents, such as amines, alcohols, etc.[1-7]

The latter methodology has been extensively investigated in the past 10 years for the formation of C–C bonds utilizing predominantly earth-abundant, non-precious metal-based catalysts. Specifically, Ni-catalyzed variants of this approach have been predominantly employed for the formation of $C(sp^2/sp^3)$–$C(sp^3)$ bonds.[1-7][8-15][16-19] However, apart from some initial reports and observations during other studies it has not been employed for the broad formation of biaryls via $C(sp^2)$–$C(sp^2)$ coupling.[20-26]

Since the privileged biaryl moiety is prevalent in a wide range of organic compounds including biologically active natural products, pharmaceuticals, agrochemicals and functional materials, among many others,[27-31] reductive coupling reactions according to modes 1. and 2. have been realized employing aryl (pseudo)halides and different Ni-catalysts.[1-7][31-36][37-40] In general, it is assumed that these Ni-catalyzed reductive coupling reactions proceed via a Ni(III)-intermediate as the key species bearing two biaryl fragments, beside a (pseudo)halide as ligands (**Scheme 1**).[41-43]



Scheme 1. Combination of previously reported reductive Ni-catalyzed coupling of aryl halides and dual Ni/photoredox-catalyzed $C(sp^2)$–$C(sp^3)$ coupling enabling our approach of dual Ni/photoredox catalyzed homocoupling towards biaryls.

On this basis we hypothesized that dual Ni/photoredox catalysis could enable a broadly applicable reductive biaryl coupling

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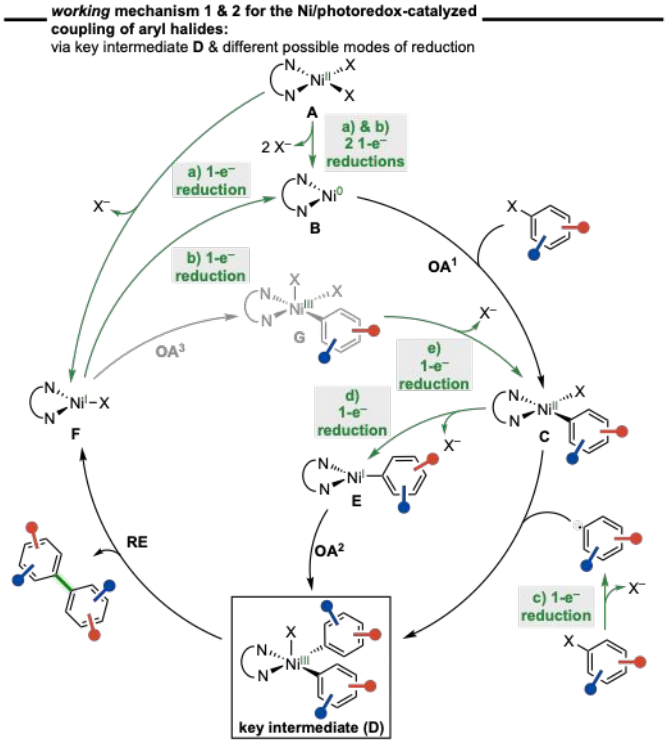
reaction under mild conditions using simple amine reducing agents, since these are easily and inexpensively available, but also energetically favourable, e.g. in comparison to metal-based reducing agents. In order to investigate our hypothesis on a simple level in this initial work, we focused on the reductive homo-coupling reaction, often referred to as Ullmann(-type) coupling, towards highly functionalized biaryls.

Results and Discussion

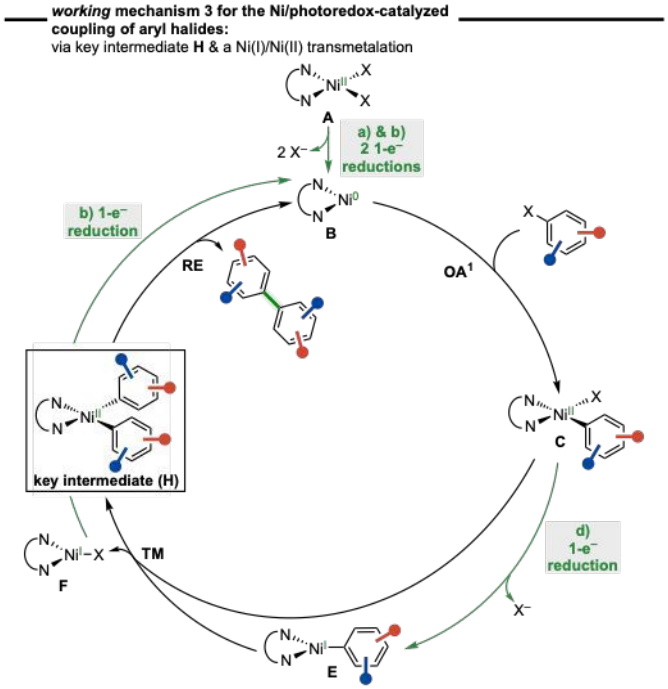
Mechanistic considerations

However, before performing experimental studies regarding our hypothesis we set-up a potential working mechanism including all plausible routes to our initially recognized Ni(III) intermediate **D**. Here, it became apparent that two possible routes might lead to the latter **D**: 1. the interception of Ni(II) aryl halide complex **C** by a previously formed aryl radical; 2. the 1-e⁻-reduction of **C** by a reducing agent generating a Ni(I) aryl complex **E**. The latter might then undergo a second oxidative addition (**OA²**) with the second aryl halide. Reductive elimination (RE) of complex **D** will then furnish our desired product and generate a Ni(I) halide complex **F**. Two possible options for the formation of Ni(II) aryl halide complex **C** are feasible: 1. Ni(I) halide complex **F** is further reduced to a Ni(0) species, which subsequently undergoes **OA¹** to form Ni(II) aryl halide complex **C**; 2. Ni(I) halide complex **F** directly undergoes **OA³** forming a Ni(III) aryl dihalide complex, which might then be reduced to the necessary Ni(II) aryl halide complex **C** (**Scheme 2**).



Scheme 2. *Working* mechanism 1 and 2 of our dual Ni/photoredox catalyzed homo-coupling reaction. RE: reductive elimination, OA: oxidative addition.

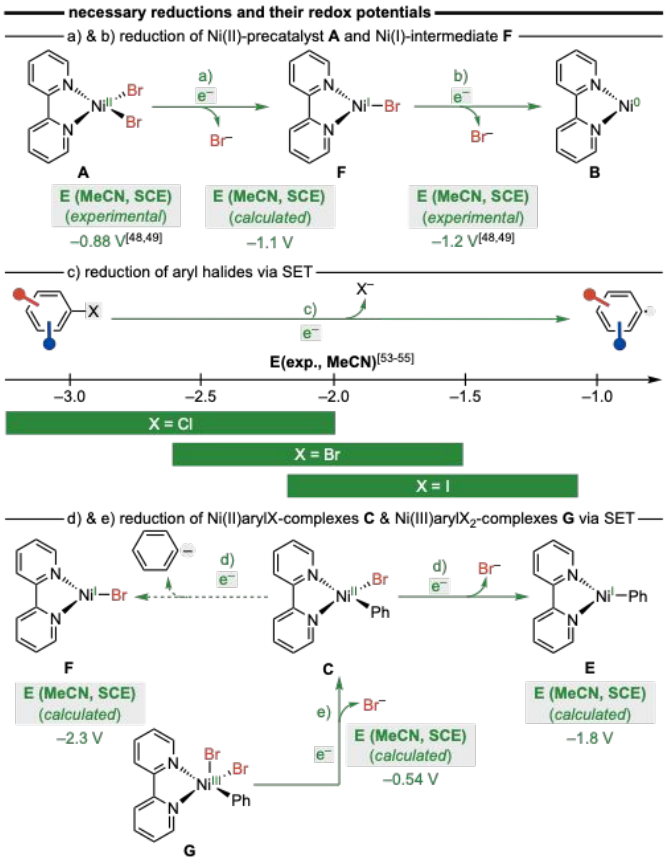
Besides these two potential pathways involving the interception of Ni(II) aryl halide complex **C** by a previously formed aryl radical or sequential oxidative additions, a possible third mechanistic option for the preparation of biaryls featuring a Ni(I)/Ni(II) transmetalation has been recently reported by Paton and Stahl.[44] in their work, they show that biaryl formation can also occur from a Ni(II) diaryl complex **H** via reductive elimination. The latter is formed via 1-e⁻ reduction of Ni(II) aryl halide **C** to Ni(I) aryl complex **E** and its subsequent transmetalation to another Ni(II) aryl halide **C**. Besides a fully different pathway regarding the formation of the desired biaryl product, this tentative mechanism exhibits the same crucial reduction steps a), b) and d) concerning the Ni-catalyst as *working* mechanisms 1 and 2 (**Scheme 3**).



Scheme 3. *Working* mechanism 3 of our dual Ni/photoredox catalyzed homo-coupling reaction. RE: reductive elimination, TM: transmetalation, OA: oxidative addition.

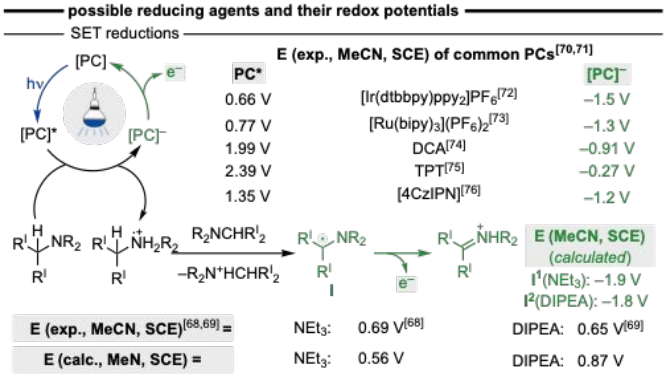
Before investigating the general viability of our hypothetic approach and the underlying reduction pathways, we thoroughly studied the literature regarding possible thermodynamic properties of the different necessary reduction steps a-e), e.g. energetics and redox potentials. Furthermore, DFT calculations regarding the reduction steps of Ni-intermediates and precursors were carried out to supplement the published experimental redox potentials E_{red} (SCE).[45,46][47,48] For the necessary reduction of the Ni(II)X_2-precursor **A**, literature precedent for both SET reductions E_{red} (exp., Ni(II)/Ni(I), MeCN, SCE) = –0.88 V[49,50] and E_{red} (exp., Ni(I)/Ni(0), MeCN, SCE) = –1.2 V[49,50] is consistent with our calculated redox potential E_{red} (calc., Ni(II)/Ni(I), MeCN, SCE) = –1.1 V[51,52], besides the fact that only moderately strong reducing agents would be required (**Scheme 4**, a) & b)). Next, the redox potentials for the reduction of aryl (pseudo) halides, which were reported in the literature, were evaluated,

providing a clear trend (X = I > Br > Cl) regarding the feasibility of radical formation.[53-55][56] It became clear that especially chlorides and electron-rich bromides would require strong reducing agents (E_{red} (MeCN, SCE) > 2.5 V) (**Scheme 4**, c)).[56] Finally, we were interested in the feasibility of the various possible reduction steps leading to key intermediates **D** and **H**. Since only limited literature precedencies were found for the required reduction steps d) and e), we again performed DFT calculations. These indicate that the reductions of Ni(II) aryl halide intermediates **C** to open-shell Ni(I) aryl complex **E** (E_{red} (calc., MeCN, SCE) = –1.8 V)[57,58], as well as the reduction of Ni(III) aryl X_2 **G** to **C** (E_{red} (calc., MeCN, SCE) = –0.54 V) are possible.[59,60] Furthermore, our calculations indicate that the selectivity of the reduction of Ni(II) aryl halide complex **C** is favoured towards the formation of Ni(I) aryl complex **E**, which is in accordance to experimental observations.[61-65] However, the feasibility of the generation of **G** exhibiting an aryl substituent and bipy ligands via **OA³** is still debated.[61-65][66] At this point, the potential pathway towards key intermediate **D** via **E** (*working* mechanisms 2 and 3*)* appears to be as plausible as that involving Ni-complex **C** and an aryl radical (*working* mechanism 1) (**Scheme 4**, d & e).



Scheme 4. Overview of significant reductions and their experimental and calculated redox potentials. DFT calculations: level of theory: PBE0/def2-TZVPP//D4/SMD(MeCN).

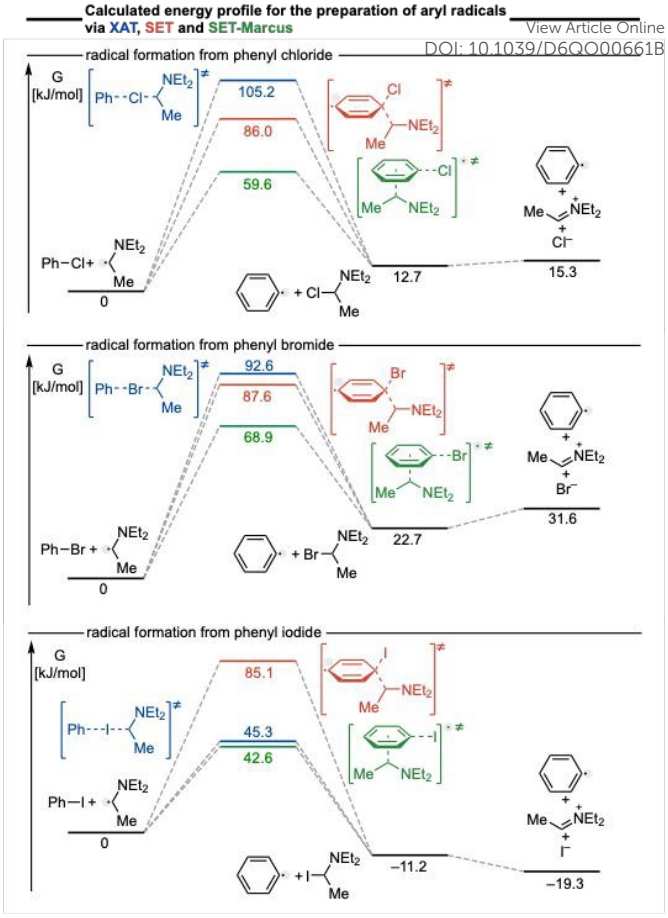
Next, potential reducing agents for the above-mentioned reduction processes were investigated via evaluation of experimental and calculated redox potentials.[67] As previously reported a reductive quenching cycle in combination with readily available amines, such as NEt_3 and DIPEA, provide in the reduced photocatalyst PC and the α-amino radical two strongly reducing species. However, therefore the activated photocatalyst has to be sufficient for the oxidation of the employed amines (E (MeCN, SCE) ≥ 0.7 V).[68,69] Photocatalysts that meet this condition, are then exhibiting a wide variety of redox potentials for their oxidation E (exp., MeCN, SCE) = –0.27 - 1.5 V) (**Scheme 4**).[70,71][72-76] Noteworthy, the reduce species $[PC]^-$ of many of these should not be able to catalyse our envisaged biaryl coupling via the above-mentioned reduction steps a)-e). On this basis and precedent literature reports we became interested in the possibility of generating an α-amino radical by deprotonation of the formed amino radical cation. The α-amino radical should then be a strong reducing agent with E (calc., MeCN, SCE) = –1.9 V (NEt_3) & –1.8 V (DIPEA) according to our DFT calculations via different modes of reduction (**Scheme 5**).



Scheme 5. Potential reducing agents and their experimental and calculated redox potential. DFT calculations: level of theory: M06/def2-TZVPP//D3Zero/SMD(MeCN).

With the feasibility of thermodynamics, more specifically the redox potentials, in mind, we focused on the kinetics of the reaction pathway via aryl radicals (*working* mechanism 1), as these should be present in higher concentrations than the alternative Ni(I) complex **E** and should therefore have a greater influence on the successful outcome. Only considering reduction pathways involving α-amino radicals, e.g. for weak photocatalysts, the *in situ* formation of aryl radicals is plausible via two possible modes: either a mechanism recently established by Leonori involving halogen atom transfer (XAT)[77,78], which is plausible especially for alkyl iodides; or a single electron transfer (SET) from the α-amino radical (or the reduced photocatalyst) into the aryl halide. To get an insight, which of the two modes are more likely, we conducted DFT calculations regarding the relative energies of the substrates, products, intermediates and transition states focusing on the influence of Cl, Br and I as leaving groups (**Scheme 6**).[79] Therefore, in addition to the XAT mechanism (blue)[77,78,80], we also considered a SET mechanisms. In this context, two options for the determination of the energies of transitions states are feasible: 1. a discrete transition state for the transfer of the single electron into the π-system (red); 2. a transition state for

the SET into the π-system and simultaneous C–X bond cleavage according to Marcus theory was also considered (green) (**Scheme 6**). In addition to the theoretical studies by Funes-Ardoiz[80], our thus performed DFT calculations show that the possible mode of activation (XAT vs. SET) of aryl radicals is highly dependent on the halide substrate. This is not surprising since the formation of phenyl radicals is more challenging form chlorides and bromides than iodides regardless of the underlying mode of activation, respectively the corresponding transition state, due to the increasing tendency of bond dissociation energies (BDE).[81-84] However, the possible generation of aryl radicals is more feasible via SET mechanisms, for bromides ($\Delta\Delta G^{\neq}$(SET/XAT) = 5.0 kJ/mol) and especially for chlorides ($\Delta\Delta G^{\neq}$(SET/XAT) = 19.2 kJ/mol).[85] Considering the energy barriers of the different transition states, the formation of phenyl radicals at rt seems to be feasible. It should be noted that a XAT mechanism cannot be ruled for the activation of aryl bromides and must be considered as the predominant mode of activation for iodides. The formation of phenyl radicals is only exergonic for phenyl iodide according to our calculations, which suggests that the aryl radical generated from aryl bromides and chlorides must be converted rapidly. Furthermore, our calculations show that the formation of dissociated iminium salts from α-amino halides is not exergonic for chlorides and bromides, but iodides, ruling it out as a substantial thermodynamic driving force for the former. In conclusion, our DFT calculations in addition to the results of Funez-Ardoiz and Leonori suggest that the envisaged photoredox-catalyzed formation of aryl radicals and subsequent trapping by a Ni(II) aryl halide complex **C** should be feasible for a broad variety of potential substrates.[77,78,80] Considering transition states for SET in addition to XAT, it becomes clear that the formation of aryl radicals might not only be depending on the choice of (pseudo)halides, but possibly also on the substitution on and in the aryl moiety as well as the size of the π-system. Noteworthy, these factors should not significantly affect the XAT transition state energies of aryl (pseudo)halides (**Scheme 6**).



Scheme 6. Potential mechanistic pathways for the formation of aryl radicals. DFT calculations: level of theory: M06/def2-TZVPP///D3Zero/SMD(MeCN).

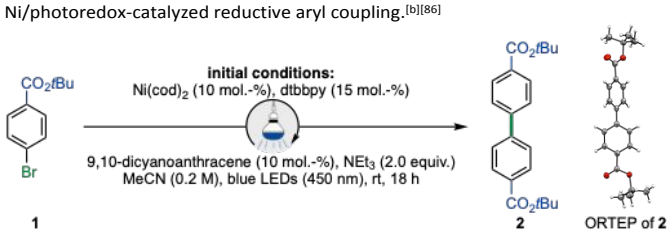
In conclusion, our preliminary theoretical considerations for a successful potential biaryl synthesis via dual Ni/photoredox-catalyzed reductive coupling have led to the following terms: 1. the redox potential of the irradiated PC* must be strong enough for the oxidation of the employed amine; 2. a high redox potential of the reduced $[PC]^-$ could be unnecessary, since the generated α-amino radical is a strong reducing agent itself; 3. the reduced $[PC]^-$ and/or the α-amino radical should be strong enough to reduce a potential Ni(II) precatalyst and Ni(I) intermediate; 4. according to the corresponding reaction pathway the aryl radical formation should be possible via either a XAT or SET mechanism depending on the chosen aryl and (pseudo)halide moiety; 5. not-considering an aryl radical pathway (*working* mechanism 1) the desired key intermediates $Ni(aryl)_2X$ (**D**) or $Ni(aryl)_2$ (**H**) must be formed via intermediate Ni(aryl) (**E**) via 1-e^--reduction of Ni(aryl)X (**C**) and subsequent Ni(II)–aryl or Ni(II)–X homolysis. Ni-complex **E** might then undergo either a second oxidative addition **OA²** towards **D** (*working* mechanism 2, **Scheme 2**) or a transmetalation to Ni(II) aryl halide-complex **C** (*working* mechanism 3, **Scheme 3**). Noteworthy, none of the aforementioned pathways for *working* mechanisms 1, 2 and 3 towards the key intermediates $Ni(III)(aryl)_2X$ (**D**) and $Ni(II)(aryl)_2$ can be ruled out at this stage. However, given the energetically favourable formation of aryl radicals under the proposed photoredox conditions, an

intersection of the Ni(II) aryl halide **C** by a separately formed aryl radical seems most plausible to us.

Experimental work

With these general considerations regarding underlying theoretical details of a potential biaryl synthesis via dual Ni/photoredox-catalyzed reductive coupling in mind, we commenced with our initial investigations (**Table 1**) starting with the homo-coupling reaction of *tert*-butyl 4-bromobenzoate (**1**) employing the organo photo-catalyst 9,10-dicyanoanthracene, which is only capable of a reductive quenching cycle (E ([PC]*) = +1.99 V, E ([PC]$^-$) = –0.91)[68,69][74], and NEt_3 (2.0 equiv.) as a reductant. Regarding the light source, a reaction setup of blue LEDs (EvoluChem™ 450 PF, 450 nm, 18 W) was used. To our delight we obtained the desired homo-coupled biaryl **2** in a promising yield of 24% (entry 1). With this result in hand, we screened a series of photoredox-catalysts exhibiting stronger potentials for the reduced species (E ([PC]$^-$ < –1.0 V). Among these, [Ir(ppy)dtbbpy]PF_6 (E ([PC]*) = +0.66 V, E ([PC]$^-$ = –1.55)[72] showed outstanding reactivity providing **2** in 66% yield (entry 2). Continuing with [Ir(ppy)$_2$dtbbpy]PF_6, we screened different bipy ligands and identified 4,4'-$(CF_3)_2$-bipy as the superior ligand resulting in 92% yield of our desired biaryl product **2** (entry 4). We were then curious if the reducing combination of our photocatalyst and NEt_3 is capable of reducing Ni(II)-salts, which are a convenient alternative to Ni(0) precatalysts, since they are less prone to oxidation and therefore typically do not have to be stored under inert conditions. Besides other successful Ni(II) precursors $Ni(DME)Br_2$ could furnish our desired biaryl product in a lower, yet satisfying yield (84%) compared to $Ni(cod)_2$. We also screened other amines as reducing agents, as well as their stoichiometry, and light sources of different wavelengths, but none of the alternatives proved to be superior. However, employing a single weak blue LED (Osram LD CQ7P-1U3U-W5-1-K, 455 nm, 450 mW) we obtained our desired biaryl in 91% yield applying our optimized conditions for the $Ni(cod)_2$-based catalytic system (entry 5).[86] Notably, all catalysts and reagents, as well as the irradiation were necessary indicated by control reactions.[867] Finally, we were already interested at this stage, if our catalytic conditions are adaptable to a larger scale employing the same instrumental setup. To our delight we obtained our desired biaryl **2** in 89% yield on a 25 mmol scale (entry 6).

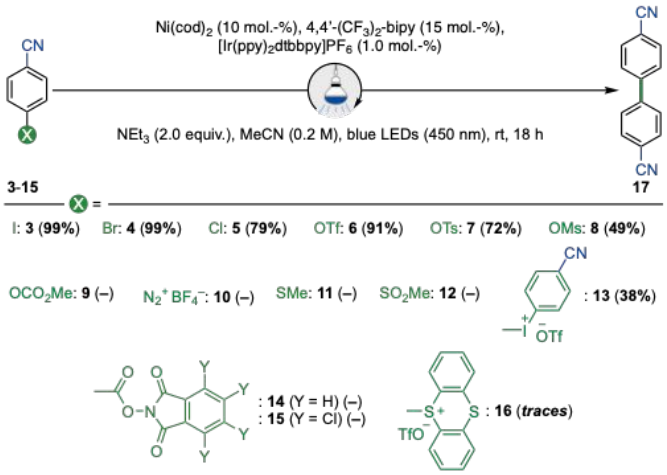
Table 1. Selected results of our optimization studies regarding the dual Ni/photoredox-catalyzed reductive aryl coupling.[b][86]



entry	changes from initial conditions	yield[a]
1	–	24%
2	[Ir(ppy)$_2$dtbbpy]PF_6 (1.0 mol.-%) was used	66%
3	[Ir(ppy)$_2$dtbbpy]PF_6 & 4,4'-$(CF_3)_2$-bipy were used	92%
4	[Ir(ppy)$_2$dtbbpy]PF_6 & 4,4'-$(CF_3)_2$-bipy & $Ni(DME)Br_2$ were used	84%
5	as entry 3, but one blue LED (455 nm, 450 mW)	91%
6	as entry 3, but 25 mmol scale & 1.0 M	89%

[a] Isolated yield. [b] Reactions were performed on a 1.0 mmol scale.

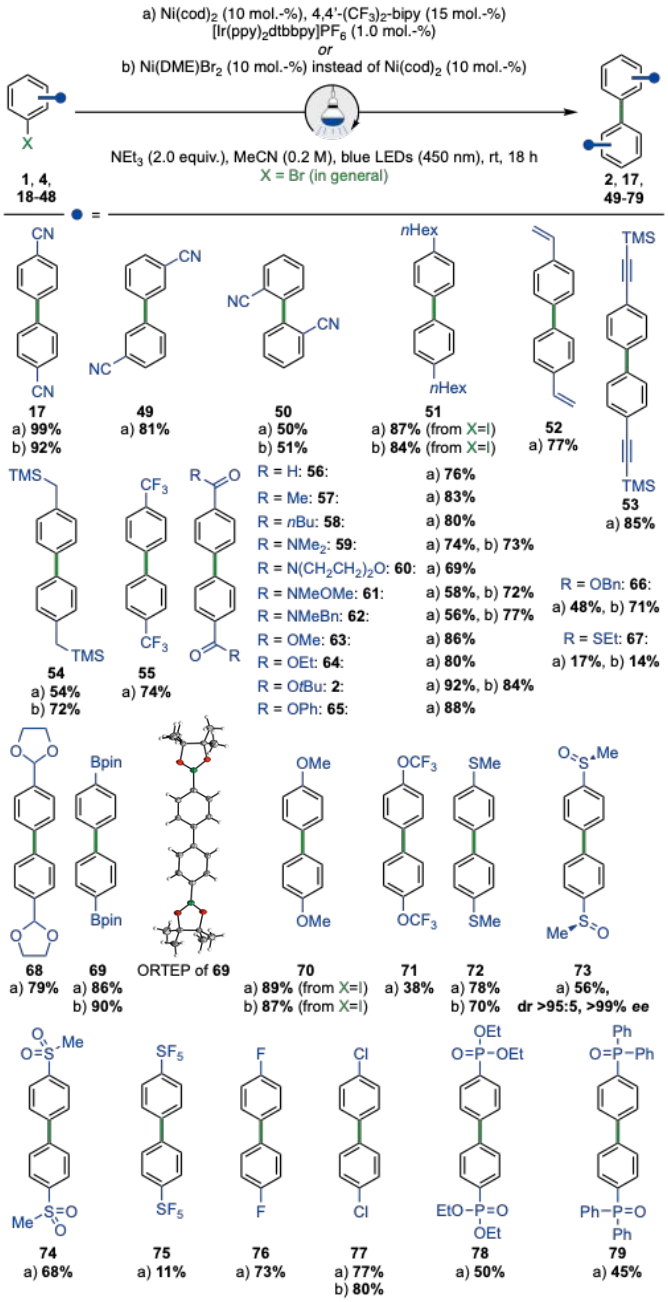
With these two catalytic conditions for a photoredox mediated homo-coupling reaction towards biaryls in hand, we next studied the scope of different potential leaving groups. Besides traditional (pseudo)halide leaving groups **3**-**9**, we also employed potential substrates with redox-active leaving groups **10**-**16**, of which only the first group **3**-**8** were suitable substrates. The observed reactivities reflect in general the expected tendencies towards oxidative addition employing a Ni(0) precatalyst since comparable yields are obtained from iodide **3**, bromide **4** and triflate **6**. Less reactive (pseudo)halides, such as tosylate **7**, chloride **5** and mesylate **8**, were also suitable, however providing our desired product **17** in decreased yields, due to lower conversions (**Scheme 7**).



Scheme 7. Screening of different (pseudo)halide and redox-active leaving groups in the dual Ni/photoredox-catalyzed reductive aryl coupling. Reactions were performed on a 1.0 mmol scale.

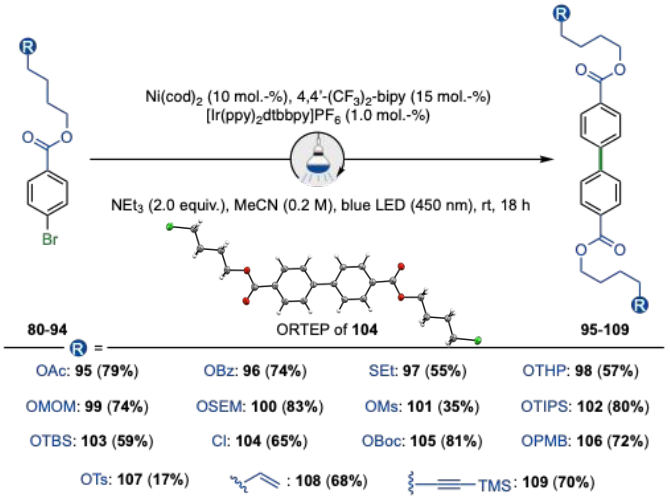
Next, we investigated the substrate scope of our newly developed homo-coupling reaction regarding different substituents on the aryl moiety. Therefore, differently mono and para-substituted aryl bromides and iodides **18**-**48** were

applied to our two general conditions. We were pleased to observe that the two conditions were applicable to a wide range of differently functionalized aryl halides including electron-withdrawing and electron-donating groups. However, for some of the obtained biaryl products **51** and **70** the corresponding iodide as the leaving group was required to achieve sufficient conversions (**Scheme 8**).



Scheme 8. Scope of the reductive homo-coupling reaction of mono-functionalized aryl bromides. Reactions were performed on a 1.0 mmol scale.

Next, we were interested in the broader tolerance regarding aliphatic functional groups and protecting groups. Therefore, a variety of esters exhibiting functionalities via a C_4-linker were tested. Again, different functional groups including alcohol protecting groups were well tolerated under our reducing reaction conditions. However, we observed diminished yields for mesylate **86** and tosylate **92**, since for these substrates major defunctionalization side-reactions occurred (**Scheme 9**).



Scheme 9. Scope of the reductive homo-coupling reaction of mono-functionalized aryl bromides exhibiting different tolerated aliphatic functional and protecting groups. Reactions were performed on a 1.0 mmol scale.

To summarize our elaborated scope of different functional groups (**Scheme 8** & **9**), a plethora of different aliphatic functional groups based on carbon **2**, **17**, **49**-**68** and **95**-**109**, boron **69**, oxygen **70** and **71**, sulfur **72**-**75** and phosphorous **78** and **79**, besides halides **76** and **77**, were tolerated well highlighting the mild reaction conditions of our reductive homo-coupling approach. (**Scheme 8** & **9**). However, some functional groups were not tolerated under our reducing reaction conditions. These include in general Brønsted acids, such as alcohols and carboxylic acids, nitro groups and amines.[88]

With these results of applicable functional groups in hand, we investigated different poly-substituted aryl bromides by submitting them to our two reaction conditions for Ni/photoredox-catalyzed homo-coupling. Again, a broad tolerance of different functional groups providing poly-substituted biaryls **127**-**143** was observed. Most noteworthy in our eyes is the formation of complex, eightfold substituted biaryl **141** in this context. However, we noticed a preliminary major limitation of our novel method as sterically demanding *ortho*-substituents were not well tolerated resulting in diminished yields due to low conversions, e.g. **133**, **138** and **143** (**Scheme 10**).

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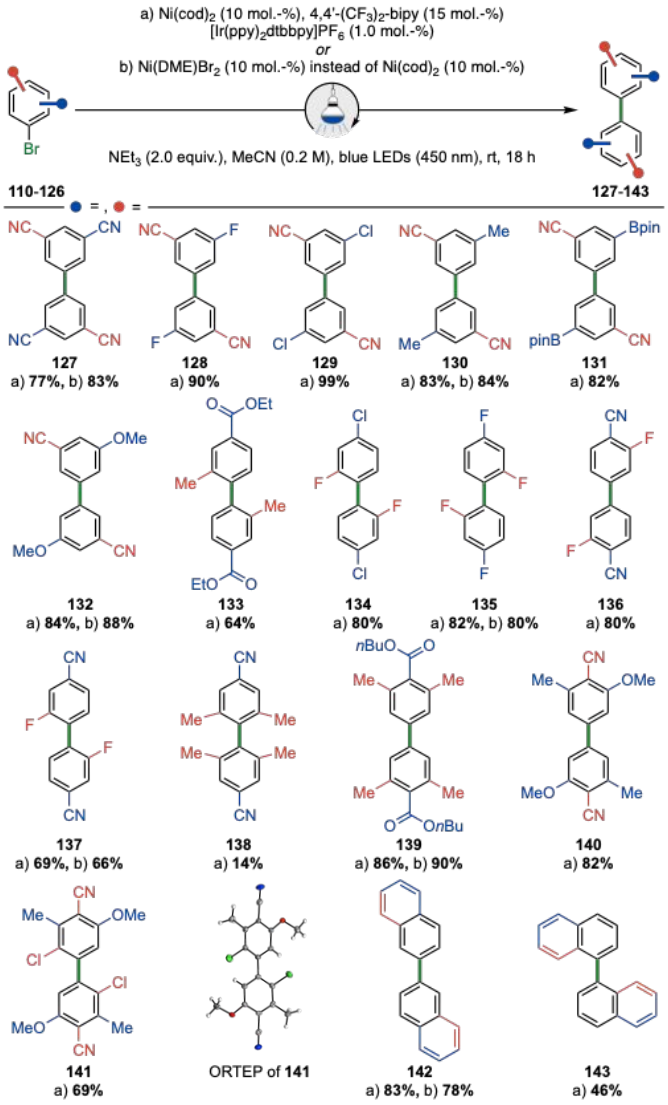
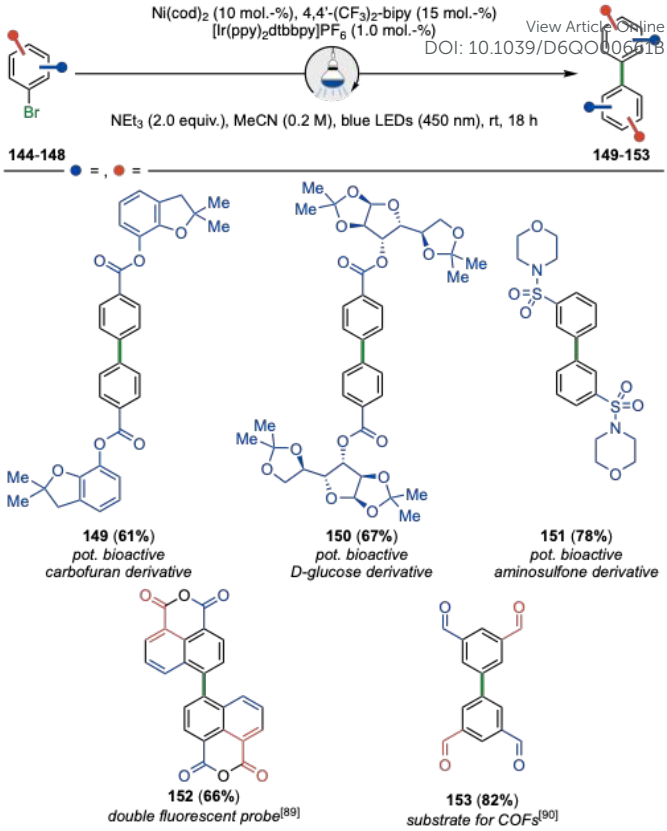


Scheme 10. Scope of the reductive homo-coupling reaction of poly-functionalized aryl bromides. Reactions were performed on a 1.0 mmol scale.

In order to highlight the synthetic value of our novel method we applied it to the synthesis of potentially useful and more complex biaryls. Different potentially bioactive products containing a carbofuran **149**, a D-glucose **150** and a sulfonamide **151** were obtained in good yields. Furthermore, the dimer of a fluorescent probe **152**[89] and the biarylic tetra-aldehyde **153** – relevant as a COF substrate[90] – were also isolated in good yields (**Scheme 11**).



Scheme 11. Synthesis of potentially useful biaryls via our reductive homo-coupling approach. Reactions were performed on a 1.0 mmol scale.

Finally, we aimed for the application of our novel method in the synthesis of symmetrical biaryl-containing hepatitis C drug daclatasvir (**154**).[91-93] Therefore, commercially available *p*-Br-phenacyl bromide (**155**) was esterified with Boc-protected L-proline (**156**) in 94% yield. Subsequently, the imidazole moiety was formed by treating the corresponding ester with NH_4OAc at elevated temperatures and the resulting NH-function was also Boc-protected providing **157** as a substrate for Ni/photoredox-catalyzed biaryl formation. The latter reaction then provided our desired biaryl **158** in 70% yield. In two further steps the Boc-groups were cleaved and the required proline-based amide function was introduced utilizing protected L-valine **159** and HATU. In summary, daclatasvir (**154**) was obtained in 26% yield over 6 steps (**Scheme 11**).

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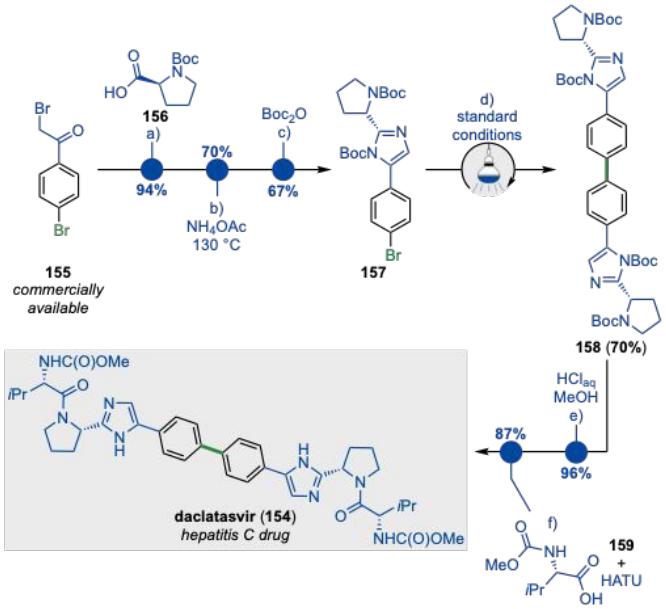
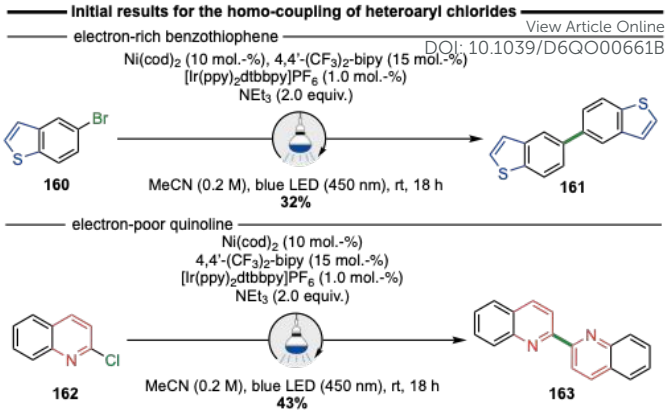


Scheme 12. Application of our Ni/photoredox catalyzed homo-coupling approach in the synthesis of hepatitis C drug daclatasvir (**155**). Reaction conditions: a) **156** (1.5 equiv.), NEt_3 (2.0 equiv.), MeCN (0.25 M), 0 °C - rt, 5 h, **94%**; b) NH_4OAc (10 equiv.), toluene (0.1 M), 130 °C, 24 h, **70%**; c) Boc_2O (1.5 equiv.), NEt_3 (3.0 equiv.), DMAP (10 mol.-%), CH_2Cl_2 (0.5 M), 0 °C - rt, 18 h, **67%**; d) $Ni(cod)_2$ (10 mol.-%), 4,4'-$(CF_3)_2$-bipy (15 mol.-%), $[Ir(ppy)_2dtbbpy]PF_6$ (1.0 mol.-%), NEt_3 (2.0 equiv.), MeCN (0.2 M), rt, 18 h, **70%**; e) HCl (6.0 M)/MeOH (1:10, 0.05 M), rt, 18 h, **96%**; f) **159** (3.0 equiv.), HATU (2.5 equiv.), DIPEA (5.5 equiv.), DMF (0.1 M), rt, 18 h, **87%**.



Scheme 13. Initial results for the dual Ni/photoredox-catalyzed reductive homo-coupling of heteroaryl chlorides.

Conclusions

On the basis of our aforementioned mechanistic considerations this work establishes a general platform for amine-driven reductive biaryl formation under dual Ni/photoredox catalysis. Expanding the latter approach from previously explored $C(sp^2/sp^3)$–$C(sp^3)$ coupling towards biaryls, 72 examples of symmetrical biaryls were prepared. In contrast to existing cross-electrophile coupling reaction towards biaryls relying on metal-based reducing agents we herein employ inexpensive and abundant amines. Furthermore, the synthetic value of our novel method was demonstrated by synthesizing various (potentially) useful products, e.g. **149**-**153** and the hepatitis C drug daclatasvir (**154**).

In the future, we will investigate the underlying reaction mechanism beyond the aforementioned general considerations (*working* mechanisms 1-3, **Scheme 2** and **3**). The simplicity of our novel method may provide deeper insights into the reactivity and mode of activation of aryl halides under reductive coupling conditions. This might also prove valuable for related fields beyond Ni and photoredox catalysis.

Besides our preliminary mechanistic studies, we have not reported herein on our investigations regarding the homo-coupling reaction of heteroaryl (pseudo)halides. Preliminary results conducted with electron-rich benzothiophene and 2-chloro quinoline already indicated the general applicability of our novel homo-coupling approach.

After further optimization of the generality of the reaction conditions for the dual Ni/photoredox-catalyzed coupling, we will report on the extension of our herein described method towards the synthesis of heterobiaryls in due course.

In this context, we are also currently exploring the application of our novel Ni/photoredox-catalyzed reductive coupling method towards the synthesis of unsymmetrical biaryls via different cross-coupling approaches. Having the aforementioned mechanistic considerations in mind, several possible options for cross-selectivity are viable, allowing for the resource-efficient and broadly applicable synthesis of valuable functionalized biaryls via cross-electrophile coupling reactions.

Author contributions

D. B. conceptualized the project. S. S., K. O., D. S. and D. B. performed the experiments and analysed the results. D. B. supervised and directed the project. K. O. and D. B. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information contains further details of the experimental procedures, ^1H and ^{13}C NMR spectra, HRMS data, and X-ray crystallographic data. CCDC 2483168, 2483169, 2483171 and 2483172 contain the supplementary crystallographic data for this paper.

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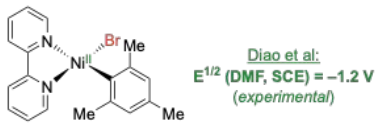

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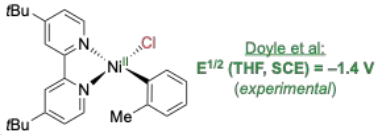

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[94] Deposition numbers 2483168 (for **2**), 2483169 (for **69**), 2483170 (for **104**), 2483171 (for **141**) and 2483172 (for (*S*)-**160**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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The data supporting this article have been included as part of the supplementary information (SI). Supplementary information contains further details of the experimental procedures, ^{1}H and ^{13}C NMR spectra, HRMS data, and X-ray crystallographic data. CCDC 2483168, 2483169, 2483171 and 2483172 contain the supplementary crystallographic data for this paper.