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Nickel catalyzed chain walking cross-electrophile coupling of alkyl and aryl halides and olefin hydroarylation enabled by electrochemical reduction

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Abstract: The first electrochemical approach for the nickel-catalyzed cross-electrophile coupling was developed. This method provides a novel route to afford 1,1-diaryllalkane derivatives from simple and readily available alkyl and aryl halides in good yields and excellent regioselectivities under mild conditions. The procedure shows good tolerance for a broad variety of functional groups and both primary and secondary alkyl halides can be used. Furthermore, the reaction was successfully scaled up to the multigram scale proving the potential for the industrial application. Mechanistic investigations suggested the formation of a nickel hydride in the electroreductive chain walking arylation which led to the development of a new nickel catalyzed hydroarylation of styrenes providing a series of 1,1-diaryl alkanes in good yields under mild reaction conditions.

Introduction

Transition metal-catalyzed cross-coupling reactions have been extensively used as powerful, selective and high-yielding methods for the carbon-carbon bond formation.^[1] In this regard, reductive cross-electrophile coupling reactions have recently gained interest. Given that the preparation and handling of sometimes hazardous organometallics can be circumvented by the direct usage of readily available electrophile precursors^[2] in combination with cheap metal catalysts, reductive cross couplings are a promising tool for atom and step economic syntheses.^[3] Alkyl halides are reactive, stable and easily accessible compounds and thus a starting material for C(sp³)-C bond formation reactions. However, due to the unproductive β -hydride elimination their application in transition metal-catalyzed coupling reactions may be limited. At the same time, this undesired feature can be utilized for selective C-H functionalizations through iterative migratory insertion/ β -hydrogen elimination sequences.^[4] These chain walking processes combined with cross-coupling strategies provide thus an attractive possibility for remote functionalization of non-activated C(sp³)-H bonds.^[5,6]

The 1,1-diaryllalkane motif is present in many biologically active natural products and relevant pharmaceuticals^[7] (Figure 1). As a result, efforts have been devoted to develop new methods for the synthesis of these important scaffolds, including

the cross-coupling of benzylic and aryl halides.^[8] As an alternative reductive nickel catalyzed ligand-controlled relay cross-coupling were reported.^[9–10] Organic electrosynthesis^[11] serves as a reliable alternative to the conventional methods and may be used to replace hazardous or/and toxic reductants and oxidants by electric current.

Figure 1. Selected examples of biologically active 1,1-diaryllalkanes.

Besides better control, electrosynthetic reactions typically proceed under milder reaction conditions and feature new or complementary reactivity and mechanistic pathways. Reinforced by the utilization of the renewable energy sources (e.g. solar energy) organic electrosynthesis aims to meet sustainability requirements by decreasing waste formation and cost reduction. Electrochemically driven metal-catalyzed cross-couplings are therefore of considerable interest.^[12] Regeneration of the active catalyst in such processes is typically controlled by the electrode material as well as by applied potential/current density. Here, we report for the first time an electrochemical and nickel-catalyzed approach for the cross-electrophile coupling involving a ligand-induced chain walking process as well as an extension to the electroreductive hydroarylation of olefins (Scheme 1).

Scheme 1. Benzylic C-H arylation through Nickel catalyzed electroreductive cross-coupling of aryl and alkyl halides and electroreductive hydroarylation.

In order to develop a convenient and straightforward process we decided to use a non-divided electrochemical cell equipped with a cathode and anode. This simple set-up was chosen as the separation of the chambers by a membrane would be more cost

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intensive and less convenient. Additionally, the only side-product would be a carbon-free metal salt which acts as supporting electrolyte during the reaction; thus, decreasing the amount of consumed energy due to increased solution conductivity. We started the development of the new method by optimizing the reaction parameters including variation of electrodes (cathodes and anodes), electrolytes, current densities, solvents, concentrations and nickel complexes for the reductive cross coupling of phenylethyl bromide **1a** with bromoanisole **2a** (Scheme 2, SI: tables; entries 1-50).

Optimization including variation of:

- electrodes: Cathode (Fe, Cu/Zn (brass), Cu, Ti, Ta, Pt, Sn, Ni, RVC, steel); Anode (Fe, Mg, Zn, Al)
- electrolytes: tetrabutyl ammonium, -phosphate, -chloride, -bromide, -benzoate, -tetrafluoroborate, -perchlorate, -acetate, cetronium bromide, lithium -bromide, -perchlorate, -tetrafluoroborate, -hexafluorophosphate, potassium bromide, magnesium bromide etc
- solvents: MeCN, DMSO, DMF • temperature
- current density: 3, 6, 10, 20 (mA/cm²) • concentration
- nickel complexes: (6,6-dimethyl-2,2'-dipyridyl)+NiBr₂ or NiI₂, neocuproin+NiBr₂; bathocuproine+NiBr₂; nickel phthalocyanine

Scheme 2. Reaction optimization of the reductive cross coupling of alkyl and aryl halides using a combined nickel and electrochemical approach.

Results and Discussion

The initial cross coupling reaction was carried out using DMA as a solvent, an iron nail as anode, an iron sheet as cathode, (6,6'-dimethyl-2,2'-dipyridyl)NiBr₂ **5** as catalyst and tetrabutylammonium tetrafluoroborate as a supporting electrolyte. Under these conditions the desired product was observed in 25% yield. Despite full consumption of both starting materials, significant amounts of homo-coupling products were obtained. Replacing iron anodes to magnesium, zinc or aluminum provided cross-coupling product only in trace amount (see SI, entries 2-4). Application of different cathode materials such as brass, copper, titanium, tantalum, platinum, tin, nickel, RVC and stainless steel showed similar results (see SI, entries 5-13). In order to keep the overall costs of the reaction as low as possible, which is particularly important for scale-up, we decided to use only iron or stainless-steel electrodes. Further tests revealed a strong current density effect (see SI, entries 14-17). High current density led to a complete decomposition of starting materials, while a decrease resulted in the desired product in 45% yield. Variation of the reagent ratio improved the yield (see SI, entries 18-21). Interestingly, the use of different supporting electrolytes had no considerable effect (see SI, entries 22-38). Due to the low price and high availability we decided to use potassium bromide for further experiments. Among the different solvents tested DMA was found to be the best reaction medium (see SI,

entries 39-41). Use of nickel acetylacetonate or nickel iodide as catalyst did not improve the reaction and desired product was obtained in 41 and 57% yield, respectively (SI entries 42-43). Applying neocuproine and bathocuproine as ligand resulted in lower yields as compared to dimethyl bipyridine (see SI, entries 44-45) and with nickel phthalocyanine no product formation was observed (SI entry 46). Importantly, increasing the concentration had positive effect and the desired 1,1-diarylethane was obtained in 80% yield (see SI, entries 47 – 48). Finally, with the change of reactant ratio the isolated yield of the desired product was increased up to 91%. With use of the optimized conditions the scope of the new electro-reductive cross coupling using various bromoalkyl-aryl and bromo(het)aryl substrates was examined (Figure 2). Variation of the electronic properties of the phenyl-alkyl bromides did not affect the reaction rate. Thus, 1,1-diphenylethanes possessing methoxy-, halide- or trifluoromethyl-group (**3b – 3f**) as well as bulkier 1-naphthalenyl residue were obtained in good to excellent yields. Notably, all of these substrates besides *ortho*-chloro substituted **3d** were formed with exceptional regioselectivity, and in many cases the linear product was not detectable in the crude ¹H-NMR spectra. Encouraged by these results, we turned our attention to the alkyl halide and examined the effect of longer chain halides on the reaction yield and selectivity. Gratefully, chain elongation from ethyl to propyl and butyl (**3h – 3j**) only slightly diminished the yield (83, 81 and 75% respectively) while the regioselectivity was not affected. Additionally, secondary alkyl bromide and indolyl-3-ethyl bromide were also successfully transformed to 1,1-diarylethanes **3k** and **3l**, respectively. Next, we tested the variation of the aryl bromide substituents. *Ortho* substitution did not have an impact on the yield and the corresponding products **3m** and **3d** were obtained in good yield. This observation also indicates that the transmetalation step (*vide infra*) proceeds when the chain walking ends at the stabilized benzylic position. The electronic properties of the aryl counter-parts have no significant influence, and use of both, electron-rich (4-dimethylamino) and electron-poor (4-fluoro) aryl bromides provided the products **3n** and **3o** in good yield. Despite the electrochemical conditions more sensitive methyl carboxylate and acetyl substituents are tolerated and corresponding products **3p** and **3q** we isolated in moderate yield with high regioselectivity. Furthermore, even the free hydroxy- and amino groups are tolerated as well. Thus, 3-bromophenol and 3-bromoaniline were converted to the corresponding 1,1-diarylethanes **3r** and **3s**. To further enhance the synthetic applicability of this electrochemical reductive coupling, boronate- (**3t**) and triflate- (**3u**) derivatives were used allowing further functionalization. Use of the bulky 9-bromo anthracene, which is widely used in organic electronics^[13] resulted in the desired products in lower yields (**3v**, **3w**). In order to widen the substrate scope heteroaryl bromides, including 2-methyl-7-bromo quinoline, unprotected bromo indoles and bromo benzofuran were successfully applied to give the desired products (**3x**, **3y**, **3z**, **3aa**, **3ab**) in good yield. In summary the newly developed electroreductive cross electrophile coupling is rather general and allows the C-H benzylation to occur with high chemoselectivity under mild reaction conditions.

Figure 2. Scope of the electro-reductive cross-coupling reaction of alkyl and aryl bromides. [a] Reaction conditions: 10 mol% of [Ni], 0.075 M KBr, 0.15 M aryl bromide (either 0.6 mmol or 2.1 mmol), 0.30 M alkyl bromide, stainless steel anode and cathode, $J = 1.5 \text{ mA/cm}^2$, $Q = 4.5 \text{ F/mol}$, isolated yields; [b] PMP – *p*-methoxyphenyl; [c] the ratio between *regio*-isomers (branched+linear) is noted in brackets, otherwise is not observed.

To get insight into the mechanism of the reductive process, cyclic voltammetry (CV) measurements were performed. Platinum, nickel and iron were used as working electrodes, along with a canonical platinum wire counter electrode, and Ag/AgNO_3 (0.01 M in 0.1 M Bu_4NPF_6 in acetonitrile) as a reference. The redox potentials of direct concerted reduction of both phenethyl bromide **1a** and bromoanisole **2a** were found to be lower than $E_{\text{Red}} = -3.0 \text{ V}$ under the conditions and were difficult to detect due to the solvent's (acetonitrile) electrochemical window. In contrast, Ni^{2+} to Ni^0 electrochemical reduction proceeds at higher potential ($E_{\text{Red}} > -2.0 \text{ V}$).^[14] The cyclic voltammogram of the nickel catalyst **5** in acetonitrile showed two reversible peaks at $E^{1/2}_{\text{Red}} = -1.0 \text{ V}$ and -1.4 V , which can be attributed to formation of the Ni^{1+} and Ni^0 -species, respectively (see SI). In order to reveal the oxidation state (Ni^{1+} or Ni^0) after the initial reduction of the Ni-catalyst **5**, preparative electrolysis with controlled potentials -1.1 V and -1.5 V vs Ag/Ag^+ were conducted. The change of cell current was recorded over time and the reaction was conducted until 4.5 F/mol of charge was passed. As expected, with a set-potential of $E = -1.1 \text{ V}$ vs Ag/Ag^+ low conversion and yield of **3a** was observed due to the low current density ($0.1 - 0.3 \text{ mA/cm}^2$). In contrast, the applied potential of $E = -1.5 \text{ V}$ vs Ag/Ag^+ caused the overall increase of the cell current up to 3 mA/cm^2 and, thus, the desired cross-coupling product was obtained.

These results attest to the generation of a Ni^0 -species essential for start and to continuation of the catalytic cycle. Further investigation of the nickel complex **5** were conducted. CV studies in DMA as a solvent and KBr as a supporting electrolyte showed a more complex behavior (see supporting information).^[15] Thus, DFT calculations for the oxidative addition step at Ni^0 were conducted (Figure 3a; computational methods, see SI). The Ni^0 was stabilized by the ligand (6,6'-dimethyl-bpy) and one DMA molecule at triplet state (**B** triplet) since the singlet state (**B** singlet) is higher in energy. Starting from this Ni^0 -species, the two different oxidative addition pathways to aryl and alkyl bromide were explored. Replacement of the DMA molecule and coordination of Ni^0 to the arene results in an increase by 4.3 kcal/mol and the electronic state switches to the singlet state (**C**). The conventional two-electron oxidative addition of aryl bromide to the Ni^0 occurs with three-membered ring transition state (**C-TS**). The overall energy barrier is 13.5 kcal/mol. Alternatively, the alkyl bromide coordinates to the Ni^0 complex **B** and the energy is elevated by 9.0 kcal/mol (**E**). Complex **E** undergoes the SET-oxidative addition via C(alkyl)-Br bond dissociation (**E-TS**) to give the Ni^{I} -Br intermediate **F** and alkyl radical (**A3**) with an overall energy barrier of 19.3 kcal/mol. Thus, the oxidative addition of Ni^0 to aryl bromide is favored, if compared to the oxidative addition of the alkyl bromide.

Figure 3. [a] DFT-computed energy profiles for the oxidative addition step at Ni^0 . Free energies in solution (in $\text{kcal}\cdot\text{mol}^{-1}$) at the SMD(DMA)-M06/Def2-TZVPP//PBE/Def2-TZVP(Ni)/Def2-SVP (other atoms) level are displayed. Selected DFT geometries are listed. Bond lengths are in Å. [b] Reaction process monitoring the formation of the β -methyl styrene and the product versus the reaction time. [c] Proposed mechanism for the remote C-H functionalization. [d] Hydroarylation proving the formation of a Ni^{II} -hydride species. [e] The use of solar energy for the reductive cross coupling.

To understand the chain walking pathway, the reaction mixture was analyzed after several intervals (Figure 3b). Formation of allyl benzene was not observed, which shows that the chain walking pathway is fast and proceeds until the more stable benzylic position is reached. The accumulation of internal olefin (β -methyl styrene) indicates that the reductive elimination is the rate determining step. Based on these observations, we propose a mechanistic pathway for the migratory Ni-catalyzed electroreductive cross-coupling reaction (Figure 3c). The reaction is initiated by the reductive generation of the Ni^0 species **I** at the cathode surface. The oxidative addition of Ni^0 to aryl bromide by

two-electron-transfer pathway followed by a one electron reduction results in the formation of intermediate **III**. The latter undergoes SET oxidative addition with alkyl bromide to generate the alkyl radical and intermediate **IV**. Subsequent one electron cathodic reduction will lead to intermediate **V**. The following alkyl radical addition to the Ni -Ar intermediate leads to the Ni^{II} -intermediate **VI**, from which Ni will undergo the chain walking process involving a β -hydride elimination to give Ni^{II} hydride **VII** and reinsertion to provide **VIII**. These steps are occurring until the thermodynamically more stable benzylic-nickel complex **IX** is formed. Subsequent, reductive elimination provides the desired

1,1-diaryllalkane cross-coupling product **3** and the active Ni^0 species. The formation of the minor linear product can be explained for cases in which the aryl moiety of the alkyl bromide is bulky (e.g. **3d**, **3g**, **3w** or **3x**) and the chain walking is slowed down.

In order to prove the proposed reaction pathway of migratory insertion, we also reacted the Ni^0 -complex with *n*-propyl bromide in the presence of the aryl bromide and allyl benzene (Figure 3d). Following initially the same pathway as in the cross electrophile coupling, the propyl bromide (Figure 3, $\text{R}=\text{H}$) would react with Ni -complex **III** via a SET oxidative addition to $\text{Ni}(\text{II})$ species **VI**. Upon β -hydride elimination the $\text{Ar-Ni}^{\text{II}}\text{-H}$ species **VII'** is formed (Figure 3c, green pathway). The *in-situ* formed Ni^{II} hydride species **VII'** subsequently undergoes an olefin exchange reaction with the allylbenzene to give **VII** along with volatile propylene. Migratory insertion provides intermediate **VIII**. The following isomerization to **IX** and reductive elimination from Ni^{II} gives the desired chain-walking hydroarylation product **3** (or **7** in the case of styrenes, Figure 4).

Based on this observation we decided evaluate the Ni -catalyzed electroreductive hydroarylation^[16] by applying a series of styrene derivatives **7a-h** and aryl bromides. In general, the electronic properties of aromatic ring did to not significantly influence on the reactivity. Electron-donating substituents at various positions of benzene ring were tolerated, leading to the corresponding products in very good yields (products **7a-c**), Figure 4). Styrene, as well as 2-vinylnaphthalene both reacted smoothly providing the 1,1-diaryllkanes in the yields of 67% and 70%, respectively (**7d-e**). Furthermore, functional groups including p- CO_2Me , OAc or the carbazole moiety were tolerated and the corresponding products **7f-h** were obtained in acceptable yields. In addition to varying the olefin we also applied different aryl bromides which again resulted in the desired diarylmethanes (**7i-n**) in good yields.

Following the successful development of the nickel catalyzed electroreductive hydroarylation as well as the electroreductive cross electrophile coupling we decided to extend the utility of our electrochemical approach. Thus, as model reaction the cross coupling was conducted using photovoltaic panels as an alternative source of electricity (Figure 3e).^[17] The reaction pattern remained the same and desired product **3a** was isolated in good yield. In order to prove practicability, a multigram scale reaction was also performed (see SI). The cell was constructed from a coaxial positioned stainless-steel rod and plate. The product was isolated in comparable yield at 75 mmol scale. For larger scale processes the price of the ligand **4** (6,6'-dimethyl-2,2'-dipyridyl) may become expensive. Thus, we decided to prepare the ligand from the much cheaper 2-bromo-6-methylpyridine and nickel bromide *in situ* (Scheme 3).^[18] The resulting solution was directly used without the catalyst isolation to afford desired 1,1-diaryllalkane **3a** in 72% (11.6 g) isolated yield. After the completed reaction the cell was easily cleaned, whereas the solvent was recovered by distillation. Thus, the system can be reused multiple times.

Figure 4. Scope of the electro-reductive hydroarylation of styrenes. Reaction conditions:^[a] 10 mol% of $[\text{Ni}]$, 0.05 M KBr, 0.1 M styrene (0.4 mmol), 0.8 M aryl bromide, stainless steel anode and cathode, $J = 3.33 \text{ mA/cm}^2$, $Q = 7.5 \text{ F/mol}$, isolated yields; [b] PMP: p-methoxyphenyl, PFP: p-fluorophenyl.

Scheme 3. Cross-coupling reaction catalyzed by nickel complex generated in situ.

Conclusion

In summary, we have developed a sustainable Ni -catalyzed electroreductive cross-coupling of non-activated alkyl and aryl bromides and a hydroarylation of styrenes and allyl benzene. The new protocols enable the synthesis of pharmaceutically relevant 1,1-diaryllkanes with good functional group compatibility and excellent regioselectivity. The described protocols have several advantages as they address limitations of traditional cross-electrophile couplings by avoiding the use of pyrophoric metal powders and over-stoichiometric amounts of sensitive organic reductants. The mechanistic studies provide insight into the reaction mechanisms and confirm that the catalytic cycles involve the generation of Ni^0 species. Furthermore, in both electroreductive reactions, the cross-electrophile coupling as well as in the hydroarylation a Ni -

hydride species is formed which allows the chain walking to proceed and to provide the desired diarylalkanes. Furthermore, the established concept could be effectively applied on multigram scale and is, therefore, readily applicable for the development of further electroreductive coupling reactions.

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Keywords: electrosynthesis • migratory cross-coupling • 1,1-diarylalkanes • nickel • β -hydride elimination

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