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Ligand-Controlled Nickel-Catalyzed Reductive Relay Cross-Coupling of Alkyl Bromides and Aryl Bromides

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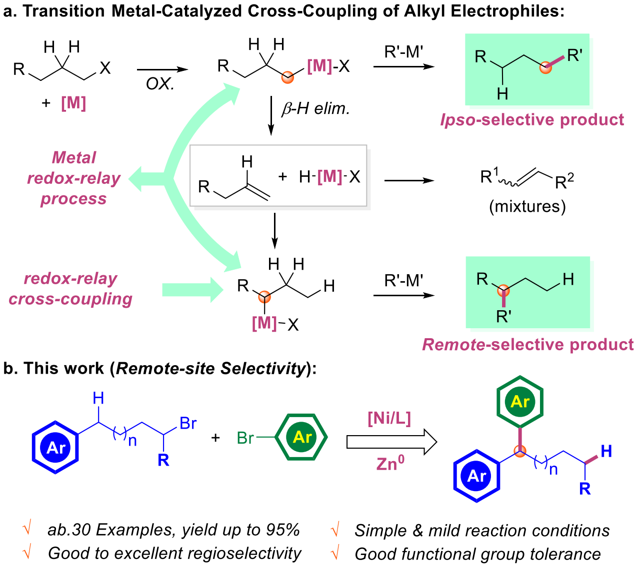
ABSTRACT: 1,1-Diarylalkanes are important structural frameworks which are widespread in biologically active molecules. Herein, we report a reductive relay cross-coupling of alkyl bromides with aryl bromides by nickel catalysis with a simple nitrogen-containing ligand. This method selectively affords 1,1-diarylalkane derivatives with good to excellent yields and regioselectivity.

KEYWORDS*: Alkyl electrophiles, β-Hydride elimination, 1,1-Diarylalkanes, Migratory cross-coupling, High-valent nickel*

Transition metal-catalyzed carbon-carbon bond formation reactions play an essential role in the synthesis of complex molecules which are relevant to pharmaceuticals, argochemicals and material sciences as highlighted by the 2010 Nobel prize in chemistry.[1] Alkyl electrophiles, which are abundant and cheap, are ideal precursors to build $C(sp^3)$-C bonds. However, coupling reactions of alkyl electrophiles are always of low efficiency due to the fact that the alkyl-metal complexes formed through oxidative addition readily undergo β-hydride elimination to form alkene side products.[2] On the other hand, taking advantage of the propensity of β-hydride elimination and the reverse, migratory insertion, to change the reacting site of alkyl electrophiles through a transition metal redox-relay process,[3] unlocks unique opportunities for *remote*-site functionalization and has recently drawn increasing attention (Scheme 1a).[4]

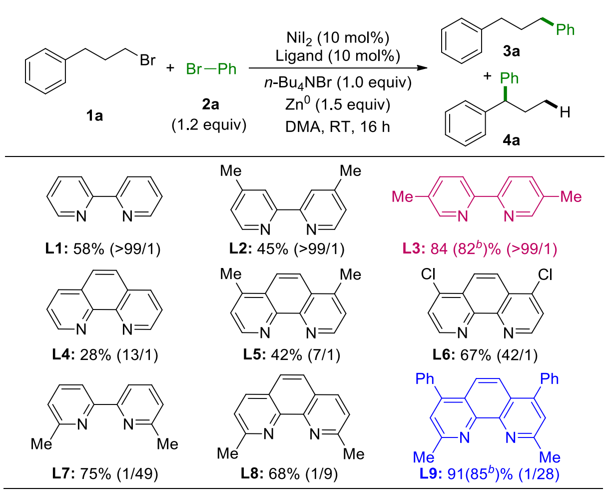
Selective cross-coupling of two different electrophiles catalyzed by earth-abundant transition metals has been well-established as a general protocol in synthesis.[5] Additionally, this strategy avoids using sensitive and dangerous metal reagents. A wide number of electrophiles have been successfully used to construct $C(sp^3)$-$C(sp^2)$, $C(sp^2)$-$C(sp^2)$ and $C(sp^3)$-$C(sp^3)$ bonds via catalysis with nickel, cobalt, or iron catalysts.[5c] Investigations on the efficiency and chemo-selectivity of reductive cross-coupling reactions have received much attention recently.[5d-f] By contrast, the regioselectivity of these transformations has been less explored and previous studies mainly report the formation of *ipso*-selective products.[5c]



Scheme 1. Transition Metal-Catalyzed Cross-Coupling of Alkyl Electrophiles

The framework of 1,1-diarylalkanes is widespread in natural products as well as synthetic biologically active molecules,[6] which has attracted many efforts towards exploration of efficient protocols to access these structural skeletons in the synthetic community. Transition metal catalysis plays an essential role in synthetic approach to these types of compounds, among which, the cross coupling of benzylic electrophiles and aryl organometallic reagents is one of the most general method.[7] However, benzylic electrophiles, especially benzylic halides are not always easy to prepare and often limited stability that prevents storage. The direct arylation of benzylic C-H bonds is an attractive protocol to access the 1,1-diarylalkanes. Recently, major progress in the synthesis of 1,1-diarylalkanes was made by Stahl[8] and Liu[9] simultaneously; they disclosed a copper-catalyzed direct oxidative arylation of benzylic C-H bonds via a radical relay strategy, with an extraordinarily broad substrate scope and good functional group tolerance. In addition, a nickel-catalyzed benzylic arylation reaction by merging nickel hydride catalyzed alkene isomerization with cross-coupling of aryl iodides was recently reported by Zhu and coworkers.[10] Herein, we report a novel reductive relay cross-coupling of non-activated alkyl electrophiles and aryl bromides by ligand-controlled nickel catalysis. This method selectively affords 1,1-diarylalkane derivatives with excellent regioselectivity and a broad substrate scope. Preliminary mechanistic investigations imply that this migratory cross-coupling transformation involves a key step of rapid Ni(III) migratory chain-walking (Scheme 1b).[11]

Table 1. Ligands Evaluation in Ni-Catalyzed Reductive Cross-Coupling of 1-Bromo-3-phenylpropane and Bromobenzene.[a]



[a] General conditions: 1a (0.2 mmol), 2a (0.24 mmol), anhydrous NiI_2 (0.02 mmol), Ligand (0.02 mmol), *n*-Bu_4NBr (0.2 mmol), Zn dust (0.3 mmol), DMA (2.0 mL), RT, 16 h; yields and ratios 3a/4a were determined by GC by using naphthalene as the internal standard. [b]Isolated yield (0.5 mmol scale).

We commenced this study with 1-bromo-3-phenylpropane (**1a**) and bromobenzene (**2a**) as the model substrates, a stable two-valent nickel salt as the catalyst and zinc dust as the reductant. After evaluation of ligands, we were delighted to find that we could tune the regioselectivity of this coupling reaction as illustrated in Table 1. Employment of bipyridines (**L1**, **L2**, **L3**), and 1,10-phenanthrolines (**L4**, **L5**, **L6**) selectively gave the *ipso*-site cross-coupling product **3a**, with 5,5'-dimethylbipyridine (**L3**) affording the best result, in 82% isolated yield and with exclusive regioselectivity. To our surprise, the reaction with 6,6'-dimethyl substituted bipyridine (**L7**) and 2,9-dimethyl substituted 1,10-phenanthrolines (**L8**, **L9**) selectively yielded the benzylic phenylation product **4a**, amongst them bathocurproine (**L9**) proved to be the most efficient with 85% isolated yield and 28/1 regioisomeric ratio on a 0.5 mmol scale. Additionally, control experiments showed that the catalyst, ligand and reductant were all crucial to the reductive relay cross-coupling reaction, and that the addition of tetrabutylamonium bromide greatly improved the yields (see SI Table S7 for details).

With optimal conditions in hand, we turned our attention to the generality of this Ni-catalyzed relay cross-coupling reaction. As shown in Table 2, *C*2-*C*5 aryl-substituted alkyl bromides were examined in the reductive relay cross-coupling transformations and all type of alkyl bromides were capable to furnish the 1,1-diarylalkane products, albeit longer carbon chain substrates with slightly lower yield. Furthermore, it was found that the electronic properties of substituents on aryl groups did not significantly affect the reactivity. A variety of functional groups such as chlorides (**4c**, **4d** and **4n**), unprotected indoles (**4h**, **4i**), amines (**4l**, **4q**), alcohols (**4r**), amides (**4k**) and electron-rich pyridines (**4l**) were all well tolerated in this *remote*-arylation reaction. Notably, aryl bromide with strong electron-withdrawing group afforded low yield and poor regioselectivity (**4u**). Secondary alkyl bromides could also give rise to the benzylic arylation products with moderate yields and excellent benzylic selectivity (**4a**, **4v** and **4w**). A gram-scale experiment (**4k**) showcased the scalability of this cross-coupling reaction.

Finally, to highlight the synthetic application of this method, a strand of *anti*-cancer isoerianin analogues were prepared starting from the commercially available and inexpensive starting materials (3,4,5-trimethoxylbromo-benzene (2.5 $/gram)) in good yields (**4n**, **4o** and **4p**).[12]

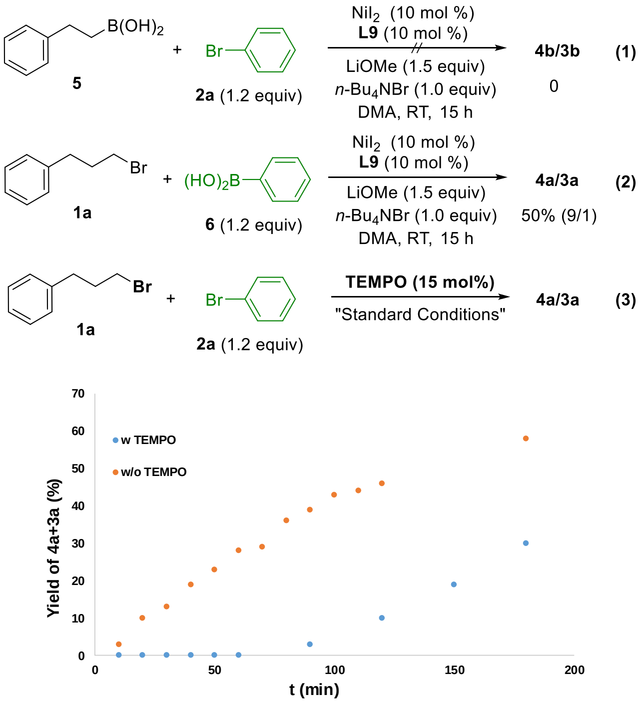
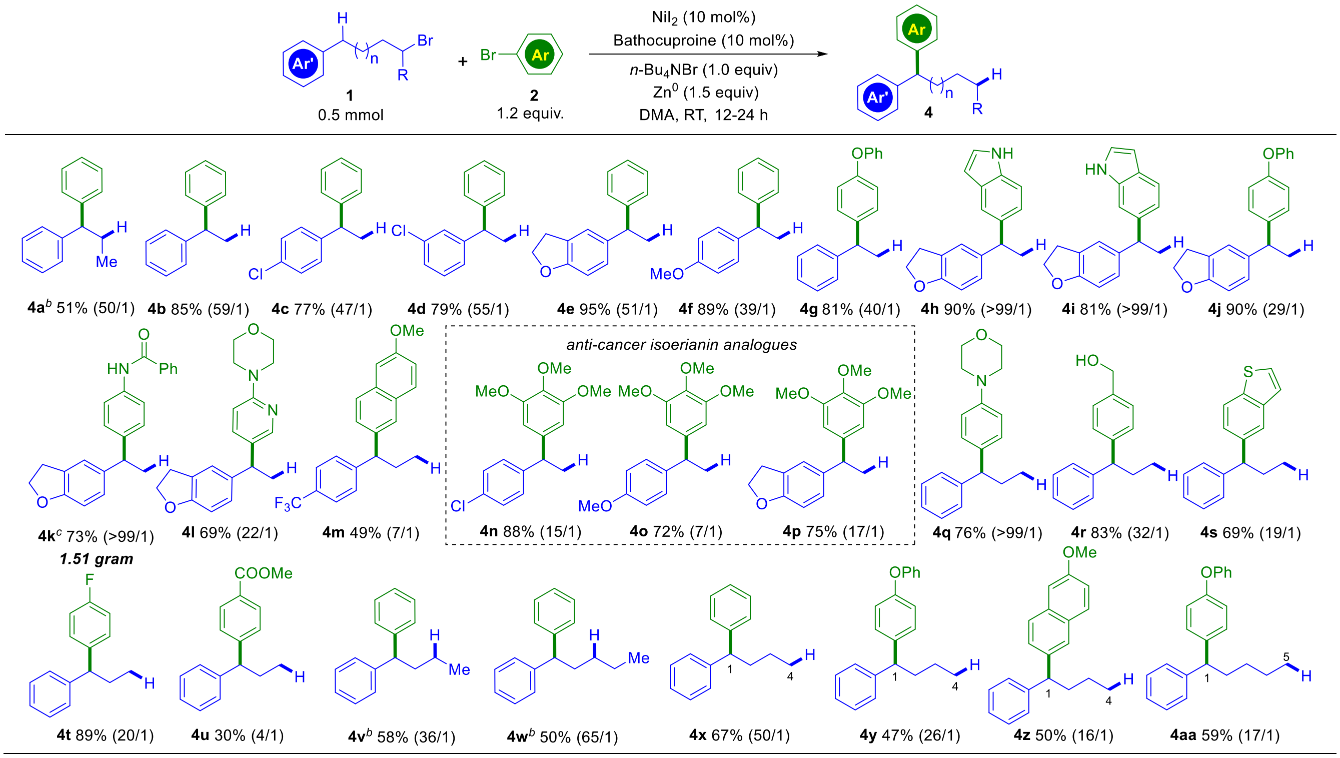


Figure 1. The Impact of TEMPO on the Reductive Relay Cross-Coupling Reactions.

In order to gain some mechanistic insights on this nickel-catalyzed cross-electrophiles coupling reaction, several control experiments were conducted (more control experiments see SI Table S8). The nickel-catalyzed Suzuki cross-coupling reaction of alkylboronic acid **5** with **2a** under redox-neutral conditions did not yield any coupling products (Eq.1), while the Suzuki reaction of **1a** with phenyl

Table 2. Scopes for Ni-Catalyzed Reductive Relay Cross-Coupling Reaction.[a]



[a] Standard conditions: **1** (0.5 mmol), **2** (0.6 mmol), anhydrous NiI_2 (0.05 mmol, 15.6 mg), Bathocuproine (0.05 mmol, 18.0 mg), *n*-Bu_4NBr (0.5 mmol, 161.2 mg), Zn dust (0.75 mmol, 49 mg), anhydrous DMA (4.0 mL), RT, 12-24 h; Isolated yield of **4**; Ratios in parentheses are regioisomeric ratio, representing the ratio of *remote-*/*ipso*-product, which determined by GC-MS. [b]from the secondary alkyl bromide. [c]6.0 mmol scale.

boronic acid (**6**) was able to furnish the coupling product in moderate yield with 9/1 regioisomeric ratio (Eq.2).[13] These results suggest that the *β*-hydride elimination and migratory insertion steps, namely the chain-walking process, probably happen on the high-valent Ni(III) species which is formed after the oxidative addition of alkyl bromide to the aryl-Ni(I)L complex.[14] We also examined the impact of TEMPO on the reductive relay cross-coupling reactions (Eq. 3). As shown in Figure 1, during the first 90 min, no cross-coupling products were detected. Then, the carbon-carbon bond formation was observed. In addition, the product of TEMPO with alkyl radical could be detected by HRMS. Comparatively, the reaction without TEMPO did not show any induction period. These results are consistent with the radical chain mechanism.[15,16]

Based on the above results and previous studies on the cross-electrophiles coupling reactions,[16] we tentatively propose a mechanistic scenario for the Ni-catalyzed reductive relay transformation as depicted in Figure 2. Firstly, the active catalyst species [Ni^0L] (**I**) is formed via reduction of the precatalyst Ni(II) with Zn dust. Then selective oxidative addition of Ni(0), by a two-electron-transfer pathway, into aryl bromide **2** generates aryl-Ni(II) intermediate **II**, which reacts with the alkyl radical generated through single-electron transfer process.[16] As a consequence, the Ni(III) intermediate is formed. Two pathways are possible in the following step: (***A***) direct reductive elimination to yield the *ipso*-coupling product **3**; (***B***) multiple rapid and reversible *β*-hydride elimination and reinsertion steps,[17] via the intermediates **IV** and **V**, during which the thermodynamically stable benzylic-Ni(III) intermediate **VI** is obtained. Reductive elimination yields the 1,1-diarylalkane **4** and the Ni(I) species **VII**. Then the nickel(II) complex **VIII** is generated from intermediate **VII**, followed by zinc dust reduction to regenerate the catalyst **I**. The experimental results imply that the ligand controls the two pathways. Pathway ***A*** is preferred in the reaction with **L3** as the ligand, while pathway ***B*** is more favorable when bathocurproine (**L9**) was used. In other words, the ligands dictate the regioselectivity of the cross-electrophile reactions.

In summary, we have developed a site-controllable reductive cross-coupling reaction by the choice of ligand. This novel protocol allows to construct the 1,1-diarylalkane pharmacophore from simple alkyl bromides and aryl bromides under mild conditions by earth-abundant nickel catalysis. In addition, it benefits from wide substrate scope, good functional group compatibility and excellent regioselectivity. The preliminary mechanistic studies suggest the transformation involves a high-valent nickel(III) chain-walking key step. Additional investigations to provide further mechanistic insights are currently ongoing in our laboratory.

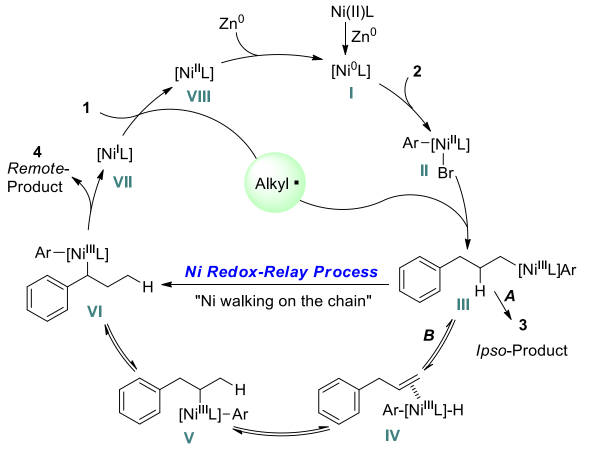


Figure 2. Proposed Mechanistic Profile for Ni-Catalyzed Reductive Relay Cross-Coupling Reaction.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org." Condition investigation, extended data about mechanism study, NMR data and characterization (PDF)

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Notes

The authors declare no competing financial interest.

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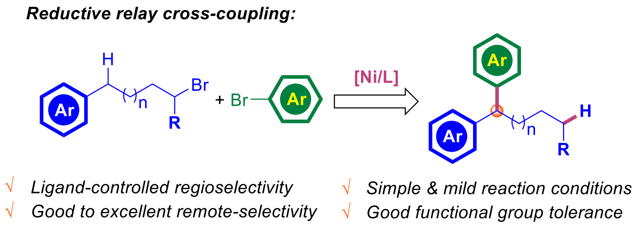
Reductive relay cross-coupling:
H
Br
n
R
Ar
+ Br
Ar
[Ni/L]
Ar
Ar
n
H
R
√ Ligand-controlled regioselectivity
√ Good to excellent remote-selectivity
√ Simple & mild reaction conditions
√ Good functional group tolerance