

Ni-Catalyzed Cross-Coupling of Dimethyl Aryl Amines with Arylboronic Esters under Reductive Conditions

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Supporting Information

ABSTRACT: Herein, we reported a successful Suzuki–Miyaura coupling of dimethyl aryl amines to forge biaryl skeleton via Ni catalysis in the absence of directing groups and preactivation. This transformation proceeded with high efficiency in the presence of magnesium. Preliminary mechanism studies demonstrated dual roles of magnesium: (i) a reductant that reduced Ni(II) species to active Ni(I) catalyst; (ii) a unique promoter that facilitated the Ni(I)/Ni(III) catalytic cycle.

N,N-Dialkyl aryl amine is an important structural motif in natural and synthetic worlds, and it is found as core structural unit in many natural products, pharmaceuticals, and organic materials.¹ At current stage, although a myriad of methods, such as Ullmann coupling reaction,² Buchwald–Hartwig amination,³ and C–H amination,⁴ on aromatic C–N bond construction have been well-developed (Scheme 1a),⁵ the reactivity pattern of *N,N*-dialkyl aryl amine is rarely investigated due to its thermodynamic and kinetic stabilities, as well as strong coordinating ability of both substrates and in

situ generated amides.⁶ For example, transition-metal catalyzed direct carbon–carbon forming cross-coupling of *N,N*-dialkyl aryl amines in the absence of directing group and preactivation has not been achieved. Triggered by the easy availability and the interest in widening the synthetic application of *N,N*-dimethyl aryl amines, we intended to explore the new transformation of *N,N*-dimethyl aryl amines through C–C bond forming cross-coupling reaction based on transition-metal catalyzed direct aromatic C–N activation. This research was also beneficial for understanding the intrinsic reactivity of aromatic C–N bond of dialkyl aryl amines.

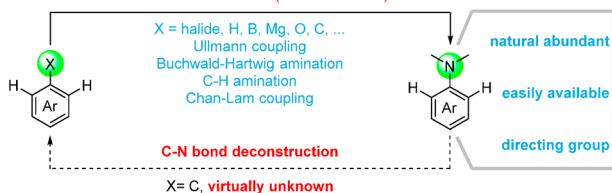
Given the commercial availability, stability, and nontoxicity of organoboron reagents, transition-metal catalyzed Suzuki–Miyaura coupling (SMC) of dimethyl aryl amines would be a suitable starting point for achieving the aforementioned goals.⁷ During the past decades, the Suzuki–Miyaura coupling reaction has been used as a powerful method to construct carbon–carbon bond from aryl halides and various O-based electrophiles.⁸ Some activated N-based electrophiles were also successfully applied into Suzuki–Miyaura coupling.⁹ For example, the cross-coupling reactions of quaternary ammonium via transition-metal catalysis have been well-documented.¹⁰ Recently, with the assistance of directing group, Kakiuchi and co-workers pioneered the research by using *N,N*-dimethyl aryl amine to construct C–C bonds through Ru-catalyzed Suzuki–Miyaura coupling. However, frequently encountered dimethyl amino group containing substrates without *ortho*-directing group remained untouched (Scheme 1b).¹¹ To the best of our knowledge, there was no reported protocol for direct Suzuki–Miyaura coupling of dimethyl aryl amines without directing group. Herein, we reported the successful catalytic Suzuki–Miyaura coupling of unmodified dimethyl aryl amines via Ni catalysis under reductive conditions (Scheme 1c).

To initiate the designed Suzuki–Miyaura coupling reaction, *N,N*-dimethyl-2-naphthalenamine (1) and phenylboronic acid neopentylglycol ester (PhBnep) (2) were chosen as coupling partners to optimize the reaction conditions (Table 1). After extensive examination of different reaction parameters, a cocktail containing NiBr₂ (10 mol %) as the catalyst, IMes^{Me} (35 mol %) as the ligand, and magnesium (3.0 equiv) as the additive in tetrahydrofuran (THF) at 135 °C facilitated the

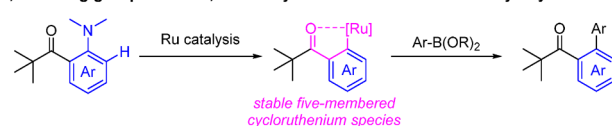
Scheme 1. Proposal for Ni-Catalyzed Suzuki–Miyaura Coupling Reaction of Dimethyl Aryl Amines

a, Construction and cleavage of aromatic C–N bond of dimethyl aryl amines

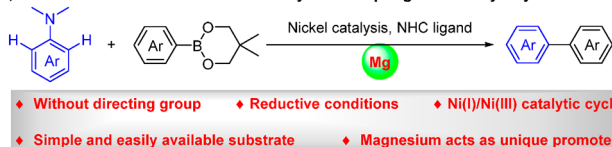
C–N bond construction (well-established)



b, Directing group-assisted, Ru-catalyzed SMC reaction of dimethyl aryl amines



c, This work: The first direct Suzuki–Miyaura coupling of dimethyl aryl amines



Received: August 15, 2018

Published: October 5, 2018

Table 1. Optimization of Reaction Conditions^a

1			2, 2.5 equiv.		"standard conditions"		3, 84%	
entry	deviation from standard conditions				yield (%)			
1	none				84 (81)		R-NMe ₂ R = R ¹	
2	without NiBr ₂				0		R-NMe ₂ R = R ²	
3	without IMes ^{Me}				0		SIMes: R = R ¹	
4	without Mg				<5		SIPr: R = R ²	
5	Ni(cod) ₂ instead of NiBr ₂				28		IMes ^{Me} : R = R ¹	
6	NiBr ₂ (DME) instead of NiBr ₂				43			
7	PCy ₃ instead of IMes ^{Me}				0			
8	IMes instead of IMes ^{Me}				14			
9	SIMes instead of IMes ^{Me}				<5			
10	IPr instead of IMes ^{Me}				0			
11	SIPr instead of IMes ^{Me}				0			
12 ^b	IMes ^{Me} (HCl) instead of IMes ^{Me}				0			
13 ^c	(PhBO) ₃ instead of 2a				<5			
14	PhBpin instead of 2a				16			
15	PhMe instead of THF				46			
16	CsF (2.0 equiv.) was added				0			

^aNMR yields were reported using CH₂Br₂ as the internal standard, isolated yield in the parentheses. ^b35 mol % ^tBuOK was added. ^c(PhBO)₃ 0.83 mmol.

desired cross-coupling, and the product 3 was detected in 84% NMR yield (entry 1). Control experiments clearly demonstrated the crucial roles of the catalyst, ligand, and magnesium for keeping the coupling efficiency (entries 2–4). Interestingly, Ni(cod)₂ and NiBr₂(DME), which were both proved active catalysts in the reported works on inert C–O and C–N bond activation, provided the desired product 3 in much lower yields (entries 5 and 6).^{8b–e,g,h,12} The effects of various ligands were also carefully investigated. Other ligands, including PCy₃, IPr, IMes, and SIMes, were submitted to the transformation to replace IMes^{Me}, but all resulted lower efficiency (entries 7–11).¹³ We also attempted to use the combination of IMes^{Me}(HCl) (35 mol %) and ^tBuOK (35 mol %) as the ligand to replace prepared IMes^{Me}, while no desired product was obtained, which might arise from the presence of ^tBuOH (entry 12). Different organoboron reagents were also examined but proved unsuitable coupling partners (entries 13–14). The examination of solvent effect indicated that nonpolar solvents were unsuitable for this transformation (entry 15). CsF, which was frequently used as an additive in Suzuki–Miyaura couplings, terminated this transformation (entry 16).^{10a}

With the optimal conditions in hand, the substrate scope was investigated. First, we tested the reactivity of different dimethyl aryl amines (Figure 1). Arylation of substrates with different alkyl substituents was conducted, and the targeted products were obtained in good yields (3–6). Arylation of substrate bearing the strained cyclopropyl ring was conducted, and the targeted product was obtained in a good yield (7).¹⁴ A collection of functional groups, such as ether and ketal, were found compatible (8–10). To our delight, alkyl-boronate was also well-tolerated (10), providing the potential for orthogonal functionalization to build complex molecules.⁷ The reactivity of other *N,N*-dimethyl amines was also investigated. For example, the arylations of *N,N*-dimethyl-1-naphthylamine and *N,N*-dimethylphenanthren-9-amine were conducted and furnished the desired products in moderate yields (11–13). Nevertheless, the steric hindrance at *ortho*-position would decrease the efficiency severely (12). The conversion of biphenyl derivatives was also investigated, and the corresponding products were obtained in satisfactory yields (14 and 15). Simple tertiary aniline was also tested but presented low

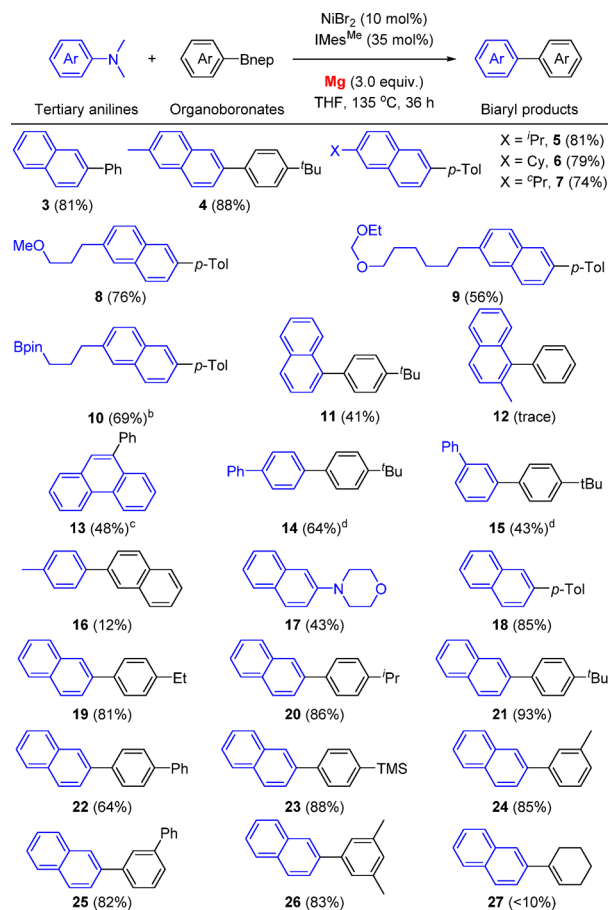


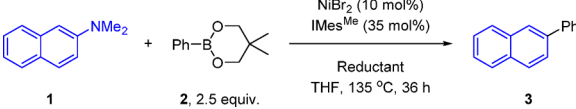
Figure 1. Catalytic SMC reaction of dimethyl aryl amines. (a) Isolated yields were reported. (b) NMR yield. (c) 46% phenanthrene was obtained. (d) 48 h.

conversion at current stage (16). Interestingly, the substrate 17, which presented high reactivity in the reported borylation protocol, exhibited a relatively low efficiency.^{12b}

Subsequently, the reactivities of different arylboronates were investigated. In general, the arylboronates bearing different alkyl substituents were proved suitable nucleophiles (18–21). Arylboronates containing phenyl substituents were also successful in the preparation of triaryl skeleton (22 and 25). Although a number of *para*- and *meta*-substituted arylboronates were successfully coupled (18–25), the *ortho*-substituted ones failed, probably caused by their steric hindrance. It is worth noting that aromatic C–B bond was superior to couple with substrate 1 than that of the aromatic C–Si bond (23). Moreover, the coupling of substrate 1 with disubstituted arylboronates smoothly delivered the biaryl compound in high yield (26). Unfortunately, at current stage, the efficient transformation of vinylboronate was not viable (27).

On the basis of the optimization experiments, we found that magnesium, which was usually used as a reductant in the transition-metal catalyzed reductive cross-coupling reaction, was crucial to promote such a Ni-catalyzed transformation in high efficiency. To our surprise, other metals with different reductive potentials, such as zinc (Zn), manganese (Mn), sodium (Na), aluminum (Al), and tin (Sn), were used as the alternatives to replace magnesium (Mg), while no desired product 3 was observed, and the substrate 1 was recovered (Table 2, entries 2–6).¹⁵ Cobaltocene (Cp₂Co),¹⁶ a common

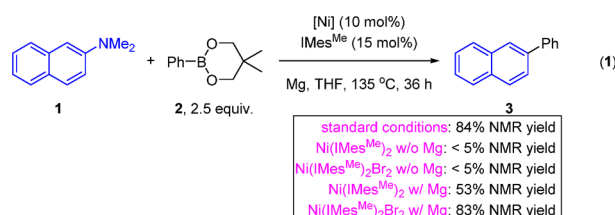
Table 2. Examination of Different Metals or Reductants^a

			
entry	metal or reductant	loading (equiv)	yield
1	magnesium	3.0	84%
2	zinc	3.0	0%
3	manganese	3.0	0%
4	sodium	6.0	0%
5	aluminum	3.0	0%
6	tin	3.0	0%
7	Cp ₂ Co	6.0	0%

^a¹H NMR yields were reported using CH₂Br₂ as the internal standard.

one-electron reducing agent, was also submitted to the catalytic cycle, while failed to promote the conversion of substrate **1** (Table 2, entry 7).

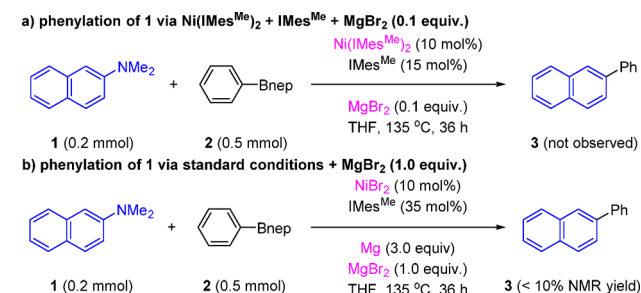
Preliminary mechanism studies were conducted to elucidate the active species in this catalytic system. As Ni(0)/Ni(II) catalytic cycles were previously proposed for a series of coupling reactions,¹⁷ both (IMes^{Me})₂Ni(0) and (IMes^{Me})₂Ni(II)Br₂ were prepared and tested as the catalysts in the coupling reaction; unfortunately, no product **3** was detected (eq 1). The addition of Mg could improve the efficiency; for



example, the product **3** was observed in 53% NMR yield for (IMes^{Me})₂Ni(0) and in 83% NMR yield for (IMes^{Me})₂Ni(II)Br₂. Since the yield of phenylation by using Ni(0) catalyst was much lower than that for Ni(II) catalyst, the following two possibilities were suggested: (1) the in situ generated MgBr₂ might facilitate the Ni(0)/Ni(II) catalytic cycle; (2) a Ni(I)/Ni(III) catalytic cycle might be responsible for this transformation rather than a Ni(0)/Ni(II) pathway.

Thus, the role of MgBr₂, which was in situ generated during the reduction of NiBr₂ to form active Ni catalyst by magnesium, was explored. As previously reported, MgBr₂ can be used as an additive to promote the efficiency of transition-metal catalyzed cross-coupling.¹⁸ To explore the effect of MgBr₂ in the transformation, catalytic amount of MgBr₂ was subjected as an additive to the catalytic system based on Ni(IMes^{Me})₂ (Scheme 2a). Unfortunately, MgBr₂ was completely inactive to promote the efficiency. Moreover, the efficiency of cross-coupling under standard conditions dramatically decreased in the presence of stoichiometric amount of MgBr₂ (Scheme 2b). These results ruled out the possibility that MgBr₂ could act as the promoter in this transformation.

Experiments to identify the Ni(I)/Ni(III) pathway was also conducted. Electron paramagnetic resonance (EPR) measurement at 10 K of the sampled reaction mixture of Ni(II)Br₂, IMes^{Me}, and magnesium, which was allowed to react at 135 °C in THF for 6 h prior to the EPR measurement, showed an axial-type signal with clear hyperfine coupling from bromide

Scheme 2. Effect of MgBr₂ in the SMC Reaction

atom (Figure 2). The *g*-values (*g*_⊥ = 2.461 and *g*_{||} = 2.010) and *A* values (*A*_⊥ = 111.3 MHz and *A*_{||} = 253.9 MHz) were

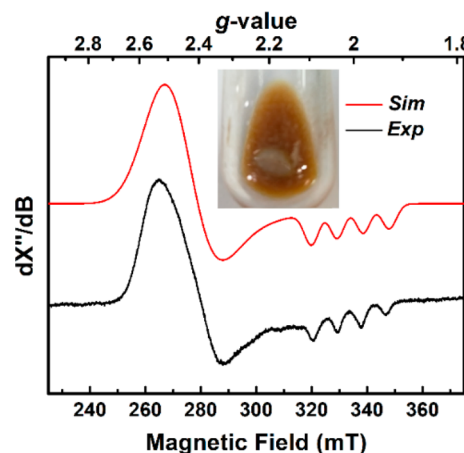
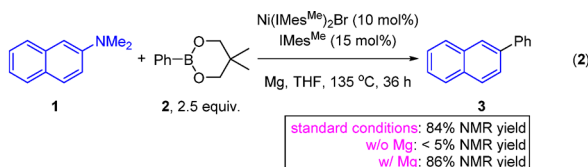


Figure 2. X-band EPR spectrum of the sampled reaction mixture of NiBr₂ (1.0 equiv.), IMes^{Me} (3.5 equiv.), and Mg (0.6 mmol) in THF heated at 135 °C for 6 h. (inset) The photo of the sample.

obtained by the simulation of the experimental spectrum using Easyspin toolbox.¹⁹ Density functional theory (DFT) calculation of (IMes^{Me})₂Ni(I)Br, which displayed a slightly distorted T-shape coordination geometry, reproduced the axial pattern of *g*-values (*g*₁ = 2.264, *g*₂ = 2.237, and *g*₃ = 2.042), and the hyperfine splitting constants of bromide atom (*A*₁ = 115.0 MHz, *A*₂ = 117.0 MHz, and *A*₃ = 249.1 MHz) were very comparable to that of the experimental values. The DFT calculation of (IMes^{Me})Ni(I)Br, another possible candidate for the key intermediate of the catalytic cycle, was also conducted; the calculated *g* (featuring rhombic pattern as *g*₁ = 2.625, *g*₂ = 2.381, and *g*₃ = 2.175) and *A* (*A*₁ = 0.8 MHz, *A*₂ = 1.0 MHz, and *A*₃ = 8.7 MHz) values were quite different from the experimental results. Therefore, the observed paramagnetic species was assigned as (IMes^{Me})₂Ni(I)Br. Mulliken population analysis revealed that 88.4% of the total spin density was localized on the Ni center in (IMes^{Me})₂Ni(I)Br, while considerable amount unpaired electron was found on Br atom (5.8%). In comparison, nearly all spin density was localized on Ni center (105.0%), and negligible amount of unpaired electron was found on Br atom (−0.5%) for (IMes^{Me})Ni(I)Br; thus, it should result in an undistinguishable hyperfine splitting of Br atom. Furthermore, a identical but weaker EPR signal was also detected for the sample of the standard reaction process, providing the solid evidence for Ni(I)/Ni(III) catalytic cycle (see Supporting Information for details).

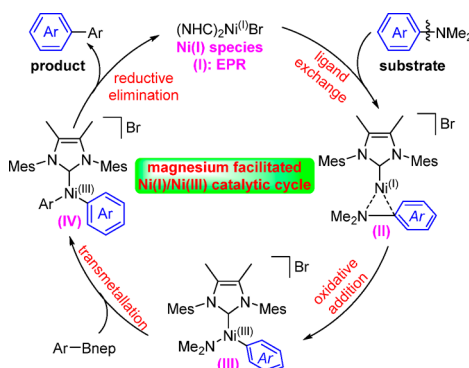
On the basis of the DFT calculations and EPR analysis, the $\text{Ni}(\text{IMes}^{\text{Me}})_2\text{Br}$ complex was prepared and submitted to the catalytic transformation; interestingly, no desired product was observed without Mg, but 86% NMR yield was obtained when 3.0 equiv of Mg was added (eq 2). These results indicated that



Mg has dual roles: (i) acted as a sufficient reductant to reduce Ni(II) to Ni(I) species, (ii) played a pivotal role in some elementary steps of the catalytic cycle.

On the basis of the aforementioned results and previously reported works,^{18,20} a plausible mechanism based on magnesium-facilitated Ni(I)/Ni(III) catalytic cycle was depicted in Scheme 3. First, the Ni(I) species II was formed

Scheme 3. Plausible Mechanism for the SMC Reaction



via the ligand exchange of active catalyst I with substrate, which led to oxidative addition of aromatic C–N to produce the Ni(III) species III. With the presence of organoboronate, the Ni(III) species IV was generated via the transmetalation. Finally, the desired biaryl product was released through the $\text{sp}^2\text{--}\text{sp}^2$ C–C forming reductive elimination on Ni(III) center to regenerate Ni(I) catalyst, thus fulfilling the catalytic cycle.

In summary, we demonstrated the first Suzuki–Miyaura coupling reaction of *N,N*-dialkyl aryl amines via nickel catalysis under reductive conditions in the absence of any directing groups and preactivation. Magnesium was proved to play dual roles to facilitate the reported cross-coupling reaction. Further experiments demonstrated that the reaction was delivered via Ni(I)/Ni(III) catalytic cycle. Efforts to investigate the detailed mechanism, to extend the substrate scope and to improve the efficiency of this transformation are undergoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b08779.

General considerations, preparation of substrates, arylation of C–N bonds, synthesis and characterization of products, tolerance of inert C–O electrophiles, mechanism studies, spectral data (PDF)

$\text{Ni}(\text{IMes}^{\text{Me}})_2\text{Br}_2$ (CIF)

$\text{Ni}(\text{IMes}^{\text{Me}})_2$ (CIF)

$\text{Ni}(\text{IMes}^{\text{Me}})_2\text{Br}$ (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support of this work by the “973” Project from the MOST (2015CB856600), NSFC (Nos. 21332001, 21431008, 21761132027, and 91645111), Shanghai City (18YF1401800 and 18JC1411300), and Fudan-SIMM Joint Research Fund are gratefully acknowledged. K. Wang (Fudan Univ.), Y. Liu (Fudan Univ.), and Z. Wang (Fudan Univ.) are acknowledged for the purification and analysis of partial substrates.

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