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General rhodium-catalyzed oxidative cross-coupling reactions between anilines: synthesis of unsymmetrical 2,2'-diaminobiaryls

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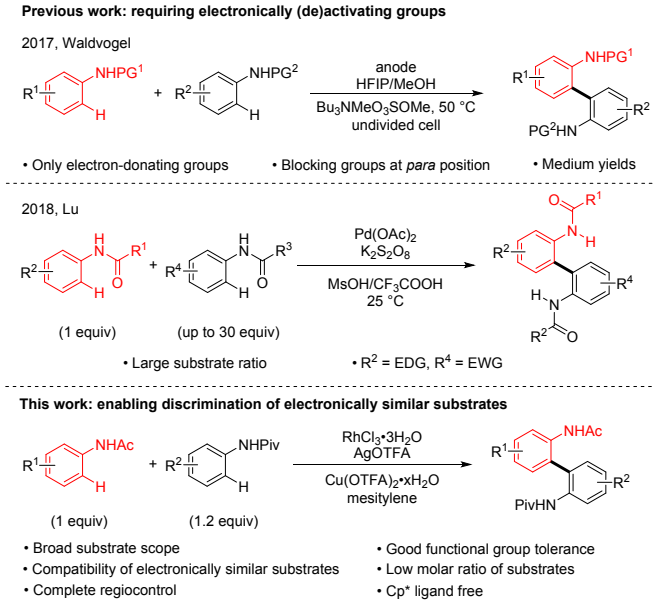
Described herein is a dual chelation-assisted $RhCl_3$-catalyzed oxidative C–H/C–H cross-coupling reaction of aniline derivatives. The highlight of this methodology is the chemo- and regioselective cross-coupling between electronically similar substrates, which represents a highly challenging task in oxidative Ar–H/Ar–H cross-coupling reactions. Furthermore, this Cp^*-Free catalytic reaction tolerates a range of functional groups and requires only a low molar ratio of coupling partners. These features expedite the synthesis of unsymmetrical 2,2'-diaminobiaryls.

2,2'-Diaminobiaryls are often found in many functional molecules such as ligands,[1] organocatalysts,[2] and synthetic intermediates.[3] Traditional methods to access the symmetric 2,2'-diaminobiaryls mainly depend on Ullmann reaction.[4] The preparation of unsymmetrical 2,2'-diaminobiaryls typically involves Suzuki-Miyaura cross-coupling reactions of *ortho*-halogenated and borylated anilines.[5] Despite reliable approaches, these methods suffer from tedious synthetic routes, limited substrate scope and large amount of toxic halide wastes. From the viewpoint of step economy and substrate availability, direct oxidative Ar–H/Ar–H cross-coupling reaction is considered as one of the most concise and efficient strategies for the construction of 2,2'-difunctional biaryls.[6] However, controlling the chemo- and regioselectivity of each coupling partners in this strategy to access unsymmetrical 2,2'-difunctional biaryls is still a highly challenging task, which mainly relies on steric and electronic effects.

In 2017, Waldvogel and co-workers reported an electrochemical C–C cross-coupling reaction of highly electron-rich anilines with a blocking group at the *para*-position.[7] Later, Lu described a palladium-catalyzed cross-coupling of anilides by employing a significant excess amount of substrate (up to 30 equivalents) to assure the output of the cross-coupled biaryl. Moreover, to ensure a high cross-coupling/homo-coupling selectivity, electronically distinct anilides were used as the coupling partners, which reduces the practicability of this methodology.[8] Thus, the development of a more general oxidative C–H/C–H cross-coupling reaction of anilines that could discriminate the subtle differences of electronic natures on substrates is demanded.



Scheme 1. Oxidative cross-coupling reactions between anilines.

The dual chelation-assisted strategy is considered as an ideal approach to control the regioselectivity for both coupling partners in oxidative Ar–H/Ar–H cross-coupling reaction.[9] Based on this strategy, we recently described a unique $RhCl_3$/TFA (TFA = trifluoroacetic acid) catalytic system to promote the oxidative cross-coupling reactions between benzamides and anilines, in which the coupling partners possess distinctly different electronical natures, by selection of a matched directing group pair.[10] In response to the challenge mentioned above, herein, we wish to disclose a dual chelation-assisted oxidative C–H/C–H cross-coupling reaction of anilines for synthesis of unsymmetrical 2,2'-diaminobiaryls by making use of a modified rhodium catalytic system. Notably, no

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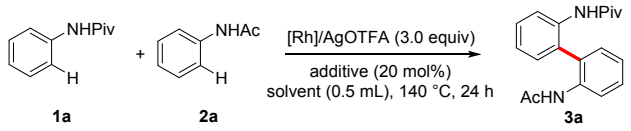
electronically activating/deactivating functional groups and blocking groups on the aryl ring are necessary, and only a low molar ratio of coupling partners is required in this reaction.

Table 1. Optimization of the reaction conditions[a]

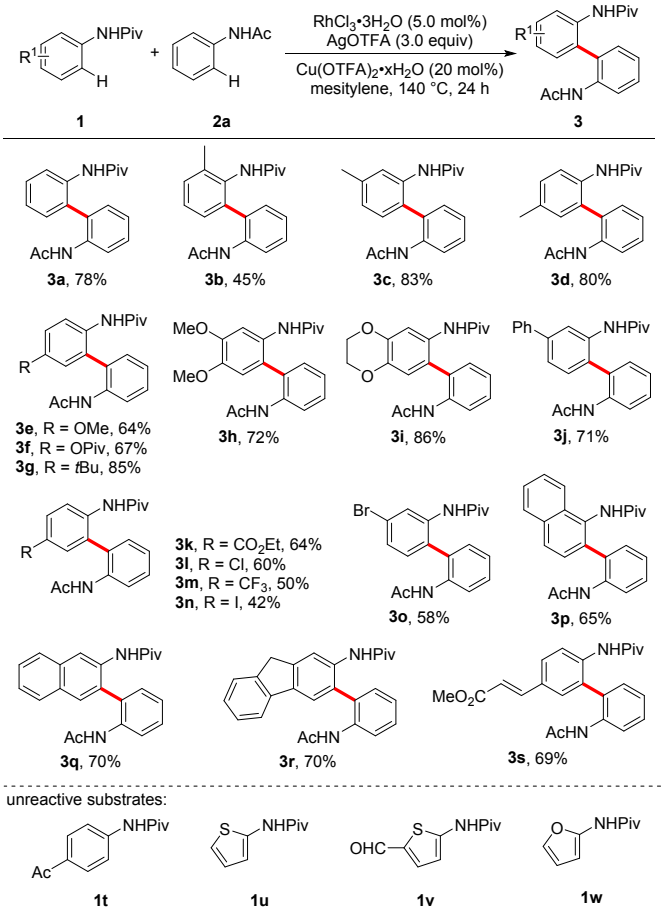


Entry	[Rh]	Additive	Solvent	Yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	mesitylene	53
2	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	1,4-dioxane	nd
3	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	DCE	nd
4	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	THF	nd
5	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	DMF	trace
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	HFIP	45
7	$RhCl_3·3H_2O$	$Cu(OAc)_2·H_2O$	mesitylene	60
8	$RhCl_3·3H_2O$	CuI	mesitylene	58
9	$RhCl_3·3H_2O$	$Cu(acac)_2$	mesitylene	trace
10	$RhCl_3·3H_2O$	$Cu(OTFA)_2·xH_2O$	mesitylene	70
11[c]	$RhCl_3·3H_2O$	$Cu(OTFA)_2·xH_2O$	mesitylene	78
12[c,d]	$RhCl_3·3H_2O$	$Cu(OTFA)_2·xH_2O$	mesitylene	67

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %) or $RhCl_3·3H_2O$ (5.0 mol %), AgOTFA (3.0 equiv), and additive (20 mol %) in solvent (0.5 mL) at 140 °C for 24 h under N_2 atmosphere. [b] Isolated yield. [c] 1.2 equiv of **1a** was used. [d] The reaction was carried out for 12 h. HFIP = hexafluoroisopropanol.

Initially, an equimolar amount of *N*-phenylpivalamide (**1a**) and *N*-phenylacetamide (**2a**), which could be readily prepared by acylation reaction, was used as the model substrate (Table 1). In the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), AgOTFA (3.0 equiv), and $Cu(OAc)_2·H_2O$ (20 mol%) as an additive in mesitylene at 140 °C, to our delight, the cross-coupled product **3a** could be obtained in 53% yield with only trace amounts of homo-coupled products (Table 1, entry 1). Next, common solvents such as 1,4-dioxane, DCE, THF and DMF were tested and proved to be ineffective for this transformation. HFIP gave a slightly inferior result, affording the desired product in 45% yield (Table 1, entries 2-6). The attempt with $RhCl_3·3H_2O$ instead of $[Cp^*RhCl_2]_2$ led to a higher yield, illustrating that Cp^* might not be crucial in this reaction (Table 1, entry 7).[11] Further screening of additives demonstrated that $Cu(OTFA)_2·xH_2O$ was the most effective (Table 1, entries 8-10). However, no reaction was detected using stoichiometric amounts of copper salts instead of AgOTFA as the oxidant, excluding the possibility of $Cu(OTFA)_2•xH_2O$ as an oxidant in this reaction (SI, Table S1, entries 14 and 15). Increasing the amount of phenylpivalamide **1a** to 1.2 equiv could further improve reaction efficiency, leading to a 78% isolated yield (Table 1, entry 11; for more details for the condition optimization, see SI). In addition, extensive exploitation of the directing groups indicated that only the pivalamido and acetamido groups are a suitable directing group pair for this reaction. The reactions using toluenesulfonamido as the directing group gave no desired product (SI, Table S2).

Table 2. Scope of *N*-phenylpivalamides[a,b]



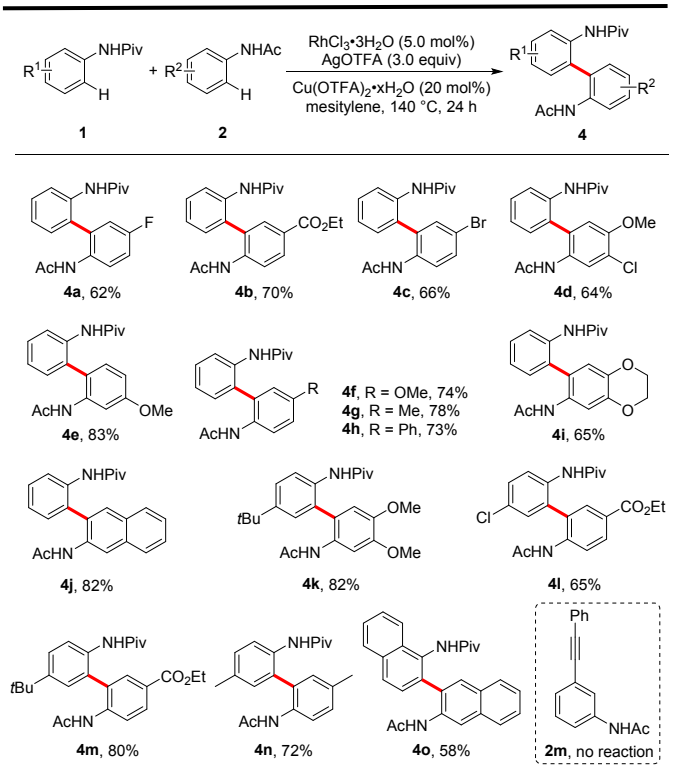
[a] Reaction was performed with **1** (0.24 mmol, 1.2 equiv), and **2a** (0.2 mmol, 1.0 equiv) in mesitylene (0.5 mL) at 140 °C for 24 h under N_2 atmosphere. [b] Isolated yield.

With the optimal reaction conditions in hand, we then explored the substrate scope of *N*-phenylpivalamides. As shown in Table 2, a variety of *N*-phenylpivalamides with substituents on *ortho*-, *meta*- and *para*-positions could work smoothly under the standard conditions to give the desired 2,2'-diaminobiaryl derivatives in moderate to high yields (Table 2, **3b**-**3d**). However, the presence of a substituent at the *ortho*-position on the phenyl ring decreased the reaction efficiency, probably owing to the enhanced steric hindrance (Table 2, **3b**). Both electron-donating groups such as alkoxy, pivaloyl, alkyl, and phenyl and electron-withdrawing groups such as ester, bromo, chloro, iodo and trifluoromethyl were accommodated perfectly (Table 2, **3e**-**3o**). In addition, α- and β-naphthylamines could also react with **2a** to deliver the biaryl products with high chemo- and regioselectivity (Table 2, **3p** and **3q**). It is worthy of note that the potentially reactive methylene and alkenyl moieties

toward oxidative conditions remained intact in this protocol (Table 2, **3r** and **3s**). However, *N*-(4-acetylphenyl)pivalamide and pivalamides contained heteroaryls such as thiophene and furan failed to undergo the desired reaction (Table 2, **1t**-**1w**).

Next, the scope of *N*-phenylacetamides was evaluated as depicted in Table 3. *N*-Phenylacetamides bearing various substituents at different positions reacted smoothly with *N*-phenylpivalamides to provide the cross-coupled products in moderate to high yields. The functional group compatibility was testified by the tolerance to fluoro, bromo, chloro, ester, alkoxy, methyl and phenyl group (Table 3, **4a**-**4i**). However, *N*-(3-(phenylethynyl)phenyl)acetamide (**2m**) proved to be an ineffective substrate to react with **1a**. *N*-(Naphthalen-2-yl)acetamide regioselectively gave a C3-arylated product (Table 3, **4j**). Finally, a set of substrates bearing substituents with similar or different electronic properties were successfully attempted (Table 3, **4k-4o**), further demonstrating the high efficiency of this unique rhodium catalytic system in the oxidative cross-coupling of electronically similar substrates and highlighting the generality of this methodology in preparing unsymmetric 2,2'-diaminobiaryls.

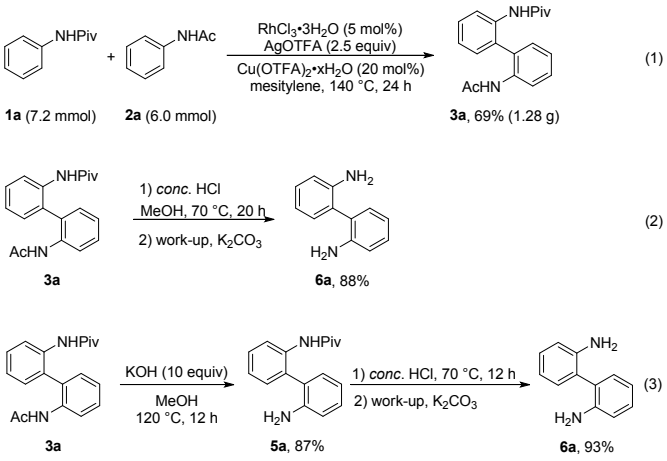
Table 3. Scope of *N*-phenylacetamide[a,b]



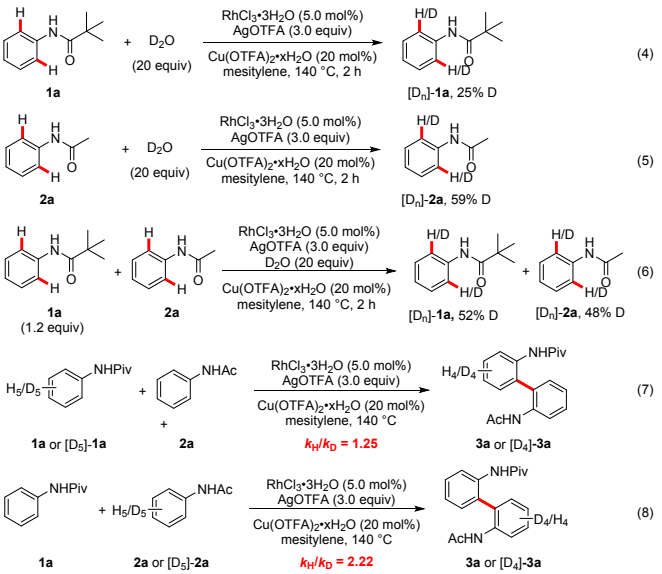
[a] Reaction was performed with **1** (0.24 mmol, 1.2 equiv), and **2** (0.2 mmol, 1.0 equiv) in mesitylene (0.5 mL) at 140 °C for 24 h under N_2 atmosphere. [b] Isolated yield.

To further illustrate the synthetic utility of this methodology, a gram-scale trial was performed, affording the target product in 69% yield (Scheme 2, eqn (1)). Moreover, the directing groups on the substrates could be simultaneously removed in the presence of HCl (Scheme 2, eqn (2)). As an alternative, the 2,2'-diaminobiphenyl could be obtained by a sequential removal of the directing groups in the presence of KOH and HCl, respectively, which provides an opportunity for further selective transformations (Scheme 2, eqn (3)).

Finally, a series of control experiments were conducted to probe the reaction mechanism. Under the standard condition, treatment of either *N*-phenylpivalamide **1a** or *N*-phenylacetamide **2a** with D_2O (20.0 equiv) led to a significant H/D exchange (25% D for **1a**, and 59% D for **2a**; Scheme 3, eqn (4) and (5)). An obvious H/D scrambling for both coupling partners was observed when a mixture of **1a** and **2a** was subjected in the presence of D_2O (52% D for **1a**, and 48% D for **2a**; Scheme 3, eqn (6)). These results indicated that the C–H activation processes of both **1a** and **2a** are reversible. Subsequently, kinetic isotope effect (KIE) experiments were conducted. A KIE value of 1.25 was observed for the parallel reactions between **1a** or [D_5]-**1a** with **2a** (Scheme 3, eqn (7)), suggesting that the *ortho* C–H bond cleavage of **1a** might not be involved in the rate-determining step. In contrast, a KIE value of 2.22 was determined when **1a** was reacted with **2a** or [D_5]-**2a** (Scheme 3, eqn (8)). This result implied the C–H activation of **2a** might be involved in the rate-determining step.

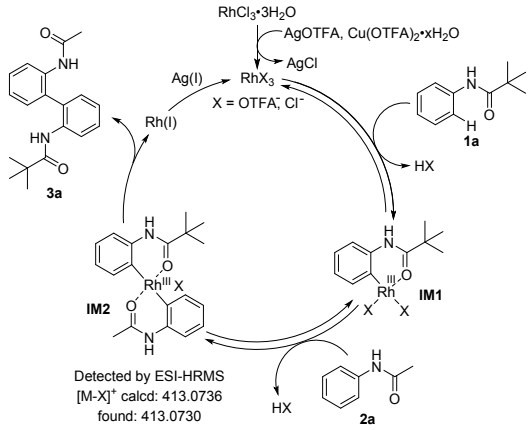


Scheme 2. Gram-scale reaction and removal of the directing groups.



Scheme 3. Mechanistic study.

Based on the above mechanistic study and previous reports,[10] a plausible pathway is proposed. Initially, a cationic Rh^{III} species is formed by chloride abstraction of $RhCl_3$ with AgOTFA in the presence of $Cu(OTFA)_2{\cdot}xH_2O$. Then a reversible directed C–H activation of *N*-phenylpivalamide **1a** might take place to give a cyclorhodium intermediate **IM1**, followed by a second directed *ortho*-C–H bond activation of *N*-phenylacetamide **2a**. The resulting bis-cyclometalted rhodium species **IM2** was confirmed by ESI-HRMS analysis (SI, Section VIII). Subsequently, **IM2** undergoes a reductive elimination to furnish the unsymmetrical 2,2'-diaminobiaryl product **3a** and release a Rh(I) species. Finally, the Rh(I) species is reoxidized to a Rh(III) species by Ag(I) to complete the catalytic cycle. At this stage, the possibility of a catalytic cycle involving C–H metalation of **2a** as the first C–H activation step cannot be ruled out.



Scheme 4. Plausible mechanistic pathway.

In summary, we have developed a dual chelation-assisted $RhCl_3$-catalyzed oxidative C–H/C–H cross-coupling reaction between *N*-phenylpivalamide and *N*-phenylacetamide, which provides a facile and general route to various unsymmetrical 2,2'-diaminobiaryls. This reaction features broad substrate scope, good functional group tolerance, low molar ratio of substrates and excellent compatibility of electronically similar coupling partners. The directing groups of the resulting 2,2'-diaminobiaryl products could be removed selectively or simultaneously. These features make this method highly applicable.

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Conflicts of interest

There are no conflicts to declare.

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General rhodium-catalyzed oxidative cross-coupling reactions between anilines: synthesis of unsymmetrical 2,2'-diaminobiaryls

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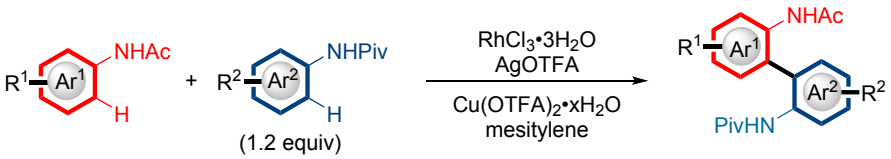

- Broad substrate scope
- Compatibility of electronically similar substrates
- Complete regiocontrol
- Good functional group tolerance
- Low molar ratio of substrates
- Cp* ligand free

Described herein is a dual chelation-assisted $RhCl_3$-catalyzed oxidative C–H/C–H cross-coupling reaction of aniline derivatives, in which the chemo- and regioselective cross-coupling between electronically similar substrates is achieved.