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Reductive Cross-Coupling between Unactivated C(aryl)–N and C(aryl)–O Bonds by Chromium Catalysis Using a Bipyridyl Ligand

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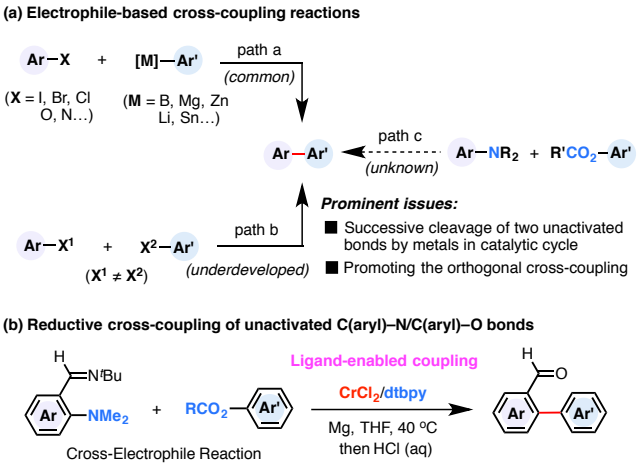
ABSTRACT: Reductive cross-coupling between two chemically inert bonds remains a great challenge in synthetic chemistry. We report here the reductive cross-coupling between unactivated C(aryl)–N and C(aryl)–O bonds that was achieved by chromium catalysis. The simple and inexpensive $CrCl_2$ salt, combined with important bipyridyl ligand and magnesium reductant, shows high reactivity in the successive cleavage of C(aryl)–N bonds of aniline derivatives and C(aryl)–O bonds of aryl esters, allowing the cross-coupling of these two unactivated and different bonds to occur in a reductive fashion to form C(aryl)–C(aryl) bond. Mechanistic studies by deuterium-labeling experiments indicate that the C(aryl)–N bonds in anilines are preferentially cleavage by reactive Cr species, in which the ligation of bipyridyl with Cr by adopting a coordination model in 1:1 ratio can be considered.

1. INTRODUCTION

Cross-coupling reactions are one of the most powerful tools in organic chemistry.[1,2] In general, nucleophiles such as organometallic or organoboron reagents are used as precursors to couple with electrophiles.[3] Recently, reductive cross-coupling using two electrophiles as partners has appeared as a powerful strategy to forge C–C bonds.[4] This cross-electrophile reaction shows high step-economy and attractive selectivity that is orthogonal to conventional strategies (Scheme 1a). Progress in the reductive coupling of aryl electrophiles with alkyl electrophiles has been made recently.[5] However, the cross couplings between two aryl electrophiles are underdeveloped and traditionally limited to classic Ullmann reactions of aryl halides.[6] Since Weix and coworkers pioneered the cross-electrophile reaction of aryl bromides with aryl triflates,[7] the use of two different aryl electrophiles as precursors in the reductive cross-coupling has attracted great synthetic and mechanistic interest.[8] Cross-electrophile reaction between two chemically inert and different aryl electrophiles by catalytic cleavage of two unactivated bonds leading to reductive coupling remains an unsolved challenge.

Aromatic C–N and C–O bonds are common in organic chemistry and although they are usually chemically unreactive, the catalytic cleavage and coupling of these bonds is of significant synthetic and mechanistic interest.[9] Elegant coupling strategies of C(aryl)–N bonds in anilines as well as C(aryl)–O bonds in esters with nucleophiles of organoboron and organometallic reagents have been developed, respectively.[10–14] We have considered whether unactivated C(aryl)–N bonds in electronically neutral anilines could undergo straightforward coupling with unactivated C(aryl)–O bonds of esters in a reductive fashion to afford C–C bonds.[15] Issues

Scheme 1. C(aryl)–C(aryl) Bond Formation via Cross-Coupling of Aryl Electrophiles



associated with this cross-electrophile reaction include: (1) the successive cleavage of unactivated C(aryl)–N and C(aryl)–O bonds by metals in one catalytic cycle, (2) promoting the orthogonal cross-coupling, and (3) inhibiting the competing homocoupling reactions in obtaining high chemoselectivity. Herein, we report a reductive cross-coupling between unactivated C(aryl)–N and C(aryl)–O bonds that was achieved by cost-effective chromium catalysis with a bipyridyl ligand, allowing for the development of a cross-electrophile reaction of chemically inert aniline derivatives with aryl esters under mild conditions (Scheme 1b).

2. RESULTS AND DISCUSSION

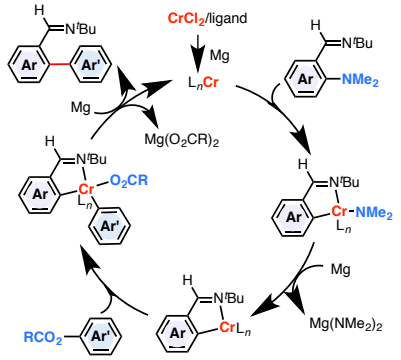
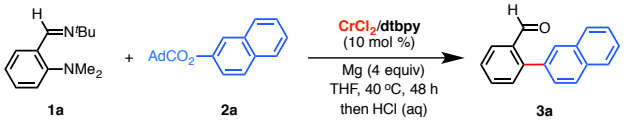


Figure 1. Working hypothesis for reductive cross-coupling of C(aryl)–N/C(aryl)–O bonds by Cr catalysis.

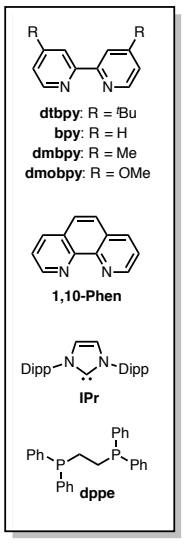
Recent advances in Cr-catalyzed reactions have encouraged us to probe the reactivity of this group 6 metal in reductive cross-coupling between two unactivated bonds.[16,17] Bullock reported that the zero-valent state of Cr could result from the reduction of Cr(II) complex with magnesium.[18] The reactive Cr can facilitate coordination with the nitrogen moiety of aniline with an *ortho*-imino chelation, by cleavage of the C(aryl)–N bond to afford cyclochromate(II) (Figure 1).[19,20] The latter may be reduced by Mg to form low-valent Cr in situ, thus, opening up the opportunity for continuous activation of the C(aryl)–O bond of an aryl ester for the orthogonal cross-coupling. Based on the mechanistic considerations, we started our research by studying the reaction of *ortho*-imino-bearing aniline **1a** with bulky 1-adamantyl aryl ester **2a** (Table 1).[10] Without external ligands, the simple $CrCl_2$ salt was an ineffective precatalyst with magnesium in promoting the cross-electrophile reaction (entry 2). The cross coupling did not occur when 2,2′-bipyridyl was used as ligand (entry 3). Gratifyingly, the electron-rich 4,4'-dimethyl-2,2'-bipyridyl showed appealing ligand behavior in assisting Cr in the successive cleavage of unactivated C(aryl)–N bond of aniline and the C(aryl)–O bond of the aryl ester, allowing for the reductive cross-coupling to occur smoothly to form the *ortho*-arylated benzaldehyde **3a** in good yield (entry 4). The use of 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbpy) improved the transformation, giving **3a** in 77% yield (entry 1). Compared with $CrCl_2$, the $CrCl_3$·3THF complex exhibited low performance in the coupling (entry 10). Other first-row metal complexes, such as $NiCl_2(PPh_3)_2$, $CoCl_2$, and $FeCl_2$, showed no reactivity in the reductive cross-coupling (entries 13–15). The replacement of 1-adamantyl group with *tert*-butyl in the aryl ester led to high conversion, affording **3a** in excellent yield (entry 16). Other C(aryl)–O bond-containing aryl electrophiles such as aryl triflate and acetate were not suitable coupling partners (entries 17 and 18).

Table 1. Studying the Effect of Ligands, First-Row Metal Salts, and Aryl Esters on Reductive Cross-Coupling[a]



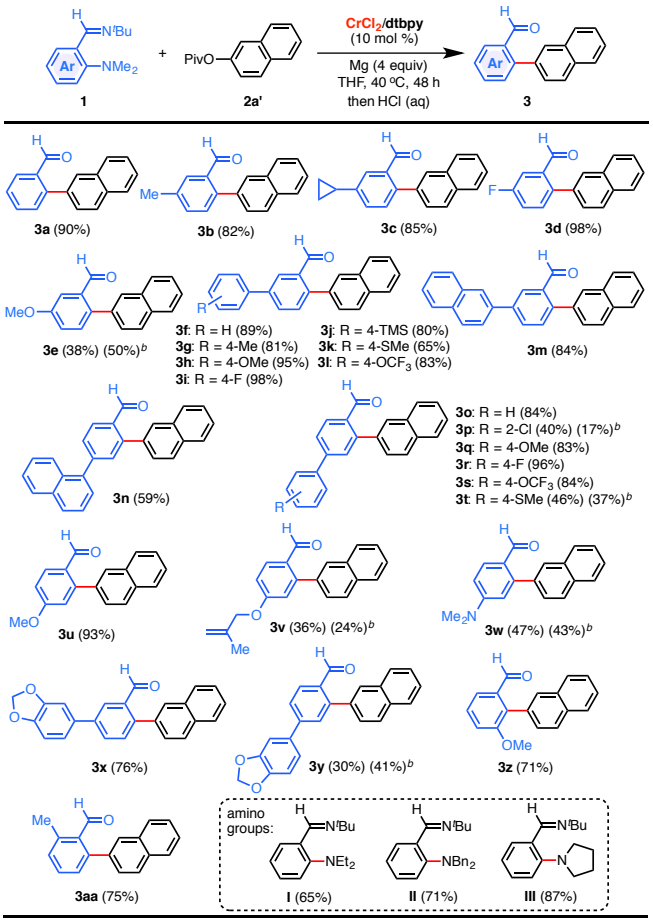
1a **2a** **3a**

entry	deviation from standard conditions	yield (**3a**)
1	none	77%
2	without dtbpy	0
3	bpy instead of dtbpy	0
4	dmbpy instead of dtbpy	62%
5	dmobpy instead of dtbpy	56%
6	1,10-Phen instead of dtbpy	0
7	IPr instead of dtbpy	0
8	dppe instead of dtbpy	0
9	without $CrCl_2$	0
10	$CrCl_3$·3THF instead of $CrCl_2$	45%
11	$Cr(acac)_3$ instead of $CrCl_2$	0
12	$Cr(CO)_6$ instead of $CrCl_2$	0
13	$NiCl_2(PPh_3)_2$ instead of $CrCl_2$	0
14	$FeCl_2$ instead of $CrCl_2$	0
15	$CoCl_2$ instead of $CrCl_2$	0
16	^{t}Bu instead of 1-Ad in **2a** (**2a'**)	90%
17	O^{t}Bu instead of 1-Ad in **2a**	13%
18	OTf or OAc instead of 1-Ad in **2a**	0
19	without Mg	0



[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), $CrCl_2$ (0.02 mmol), dtbpy (0.02 mmol), Mg (0.8 mmol), THF, 40 °C, 48 h; and then quenched with HCl (aq), 0.5 h.

Scheme 2. Reductive Cross-Coupling Between Unactivated C(aryl)–N and C(aryl)–O Bonds Using dtbpy Ligand with Cr[a]



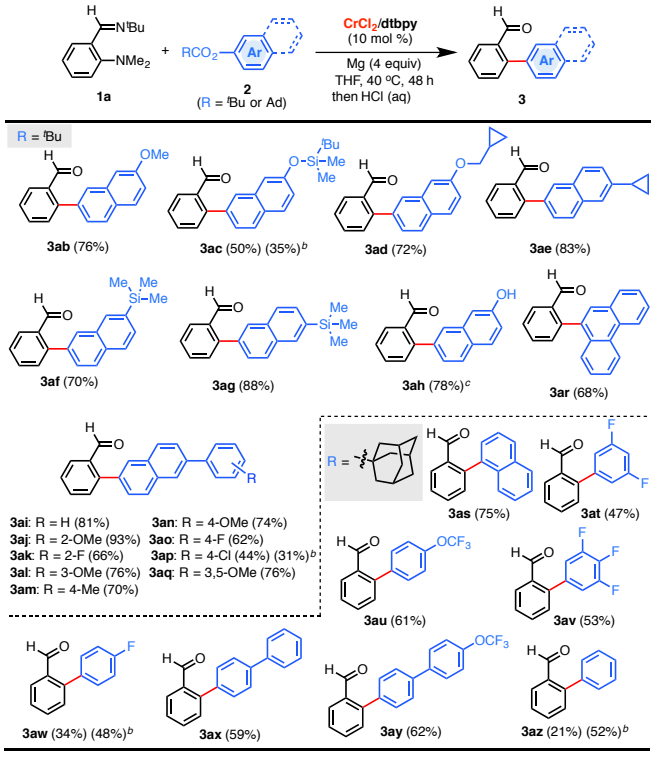
[a]Reactions were conducted on a 0.2 mmol scale. Isolated yields are given. [b]Recovery of aryl aldehyde containing an *ortho*-C–N bond.

The scope of the reductive cross-coupling between C(aryl)–N and C(aryl)–O bonds was examined. Aniline derivatives containing methyl or cyclopropyl substituents reacted with aryl ester smoothly, forming the corresponding *ortho*-arylated benzaldehydes (Scheme 2, **3b** and **3c**). Compared

with electron-rich arene (**3e**), the C(aryl)–N bond in electron-deficient arene facilitates the coupling with C(aryl)–O bond in giving high conversion (**3d**). The incorporation of either electron-rich or electron-poor aryl scaffolds into anilines did not greatly influence the cross-electrophile coupling, providing access to substituted aldehyde-bearing teraryls **3f**–**t** in moderate to excellent yields. In contrast to methoxy-substituted aniline (**3u**), the reaction with allyloxy-containing electrophiles formed the coupling product in a relatively low yield (**3v**). The cross-coupling showed high site-selectivity, with the *ortho*-C(aryl)–N bond being arylated, allowing the amino substituent at other positions to be maintained intact. The method provides a strategy to access amino-substituted and aldehyde-containing biaryl **3w**. The application of this strategy to the preparation of benzo[*d*][1,3]dioxol-5-yl-bearing compounds was also successful (**3x** and **y**). The incorporation of methoxy into the ortho position of amino did not influence the cross-coupling of C(aryl)–N bond to afford the product **3z**. Whereas the use of *ortho*-phenyl-substituted aniline derivative formed the related coupling product in trace amount of yield. The methyl at the another ortho position of imino has no effect on the reductive coupling, giving 2,6-disubstituted benzaldehyde **3aa** in 75% yield. The reactions were inhibited by the replacement of methyl with phenyl and dimethylamino group, indicating that the ortho substituents to both the amino and imino scaffolds could impact on the reductive cross-coupling of C(aryl)–N bonds. Beside dimethyl amino, the C(aryl)–N bonds in diethylamino, dibenzylamino, and pyrrolidinyl coupled with C(aryl)–O bonds of esters smoothly under Cr catalysis (**I**–**III**).

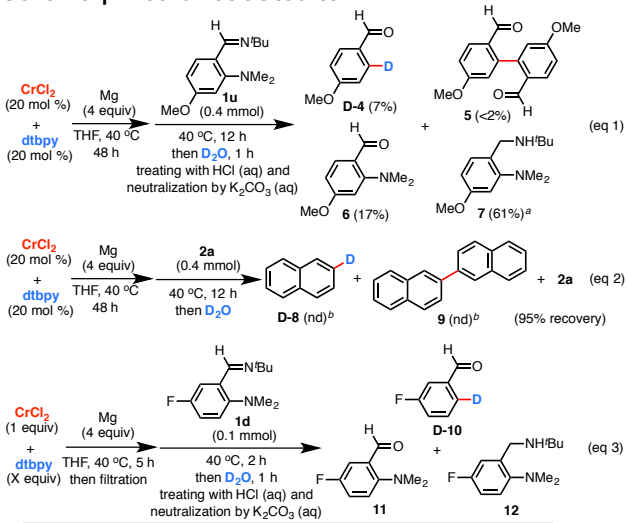
The installation of substituents such as alkoxy, silyloxy, cyclopropyl and trimethylsilyl groups onto the arenes did not affect the cross-electrophile reaction of aryl esters with aniline **1a** (Scheme 3, **3ab**–**ag**). When the use of (tetrahydro-2*H*-pyran-2-yl)oxy-substituted naphthyl pivalate, the reaction formed the related hydroxyl-containing coupling product **3ah** after workup with acid. The C(aryl)–O bonds in 2-naphthyl esters bearing substituted phenyl groups coupled with C(aryl)–N bonds effectively, providing access to benzaldehyde derivatives **3ai**–**aq**. Phenanthren-9-yl-substituted ester allowed the coupling with aniline to form **3ar** in good yield. The reductive cross-coupling of 1-naphthyl or phenyl pivalate ester with **1a** did not take place. The formation of 1-naphthol or phenol (ca. 25% yield) by the cleavage of (O)C–O bonds was observed. In contrast, the C(aryl)–O bond in 1-adamantyl-substituted 1-naphthyl ester coupled with C(aryl)–N bond effectively to furnish **3as**. Only a trace amount of naphthol was detected in the reaction (<3% yield). The reductive cross-coupling with 1-adamantyl phenyl esters containing fluoro, polyfluoro, trifluoromethoxy, or substituted phenyl scaffolds occurred smoothly under mild conditions (**3at**–**ay**). Relatively low conversion was obtained in the transformation of the C(aryl)–O bond of 1-adamantyl phenyl

Scheme 3. Cr-Catalyzed Reductive Cross-Coupling of Unactivated C(aryl)–N/C(aryl)–O Bonds[a]



[a]The coupling with 1-adamantyl aryl esters was carried out by using 20 mol % of $CrCl_2$/dtbpy at 60 °C. [b]Recovery of aryl aldehyde containing *ortho*-C–N bond. [c]7-((Tetrahydro-2*H*-pyran-2-yl)oxy)naphthalen-2-yl pivalate was used.

Scheme 4. Mechanistic Studies



X	Yield (**D-10**)[a]	Yield (**11**)[a]	Yield (**12**)[a]
1	20%	6%	65%
2	7%	10%	71%
3	2%	12%	75%

[a]GC yields were given using *n*-tridecane as internal standard. [b]Not detected by GC/MS analysis.

ester (**3az**).

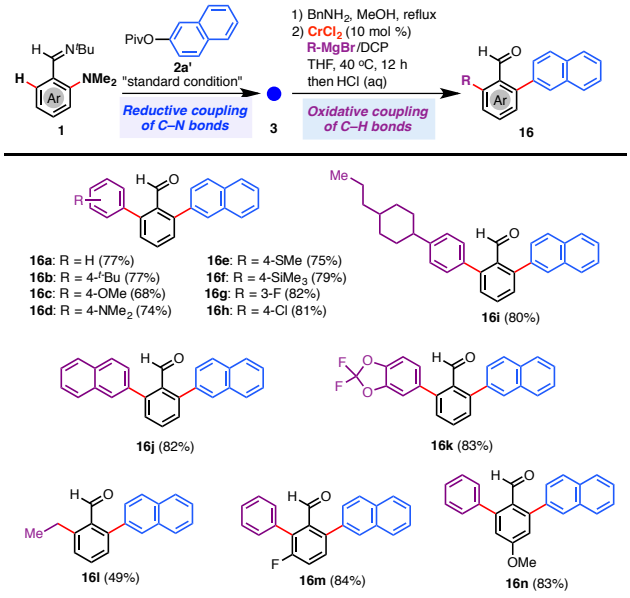
To obtain mechanistic insight into which bonds are preferentially broken with Cr, deuterium-labeling experiments based on the reaction of aniline (**1u**) and aryl ester (**2a**) with Cr species were performed, respectively (Scheme 4). By quenching the reaction of **1u** with reactive Cr that was formed in situ with D_2O, the deuterated compound (**D-4**), formed by the cleavage of C(aryl)–N bond, was identified, accompanied by a trace amount of homocoupling compound **5** (Scheme 4, eq 1). In contrast, the deuterated species of C(aryl)–O bond cleavage and homocoupling product were not detected upon reaction with the aryl pivalate (eq 2). The preferential cleavage of C(aryl)–N bond in aniline by Cr with an imino chelation can be considered. Subsequently, we carried out the stoichiometric reaction of $CrCl_2$/dtbpy with Mg followed by treatment with fluoro-substituted aniline **1d** (eq 3). After the mixture was stirred at 40 °C for 2 h and quenched with D_2O, the deuterated compound **D-10** was formed in 20% yield, by the cleavage of C(aryl)–N bond. The formation of reactive low-valent Cr that was then ligated with aniline for the breakage of C(aryl)–N bond can be considered. The increase of the amount of dtbpy ligand to 2 or 3 equivalents led to a very low yield of **D-10**. A saturated coordination of Cr with dtbpy may be unfavorable to breakage of the C(aryl)–N bond. Compared with these, the reduction of the Cr complex that was formed by stoichiometric reaction of $CrCl_2$, **1a** and dtbpy using Mg gave the benzylic amine **15** by reduction of the imino scaffold, indicating that reducing aniline-supported Cr(II) species by Mg cannot lead to the cleavage of C(aryl)–N bonds.

To further understand the ligand behavior, the influence of the amount of dtbpy on the reductive cross-coupling was studied. Increasing the amount of dtbpy resulted in low conversion for **3a**. The reaction was completely inhibited when 40 mol% of dtbpy was used (eq 5). The formation of off-cycle resting Cr species is proposed upon the addition of excess dtbpy, which may be ligation saturated and not have additional sites available to coordinate with the amino/ester groups for the cleavage of the C(aryl)–N/C(aryl)–O bonds. Interestingly, by initial treatment of $CrCl_2$/Mg with 21 mol% of dtbpy for overnight and then adding the resulting solution to the reaction mixture, only a trace amount of **3a** was detected (eq 6). The ligation of dtbpy with Cr by adopting a coordination model in 1:1 ratio to afford reactive species can be considered.

Considering that the arenes contain *ortho*-C(aryl)–N and C(aryl)–H bonds adjacent to the imino group, we next probed the possibility of sequential transformations of these unactivated bonds for the synthesis of *ortho*-disubstituted benzaldehydes with Cr catalysis. By the reaction of **1a** with naphthyl pivalate under standard conditions, the reductive coupling between C(aryl)–N and C(aryl)–O bonds gave naphthylated compound **3a**, which was isolated and further treated with Grignard reagents under Cr catalysis (Scheme 5). The substituted aryls that contain *tert*-butyl, methoxy, amino, thiomethyl, trimethylsilyl, fluoride and chloride were incorporated into the another ortho position of imino group, giving *ortho*-diarylated benzaldehydes **16a**–**h** in 68–82% total yields. The Cr-catalyzed sequential functionalization of *ortho*-C(aryl)–N and C(aryl)–H bonds was used in the preparation of 4-propylcyclohexylphenyl- and naphthyl-substituted motifs **16i** and **j**. The reductive coupling of C(aryl)–N bond followed by an oxidative coupling of C(aryl)–H bond with installation of heterocyclic 2,2-difluorobenzo[*d*][1,3]dioxolyl was successful (**16k**). In addition, selective incorporation of aryl and aliphatic scaffolds by this protocol led to the formation of 2-ethyl-6-(naphthalen-2-yl)benzaldehyde **16l**. Trisubstituted benzaldehydes bearing naphthyl, phenyl, and fluoride/methoxy in the arenes were accessible using the strategy (**16m** and **n**).

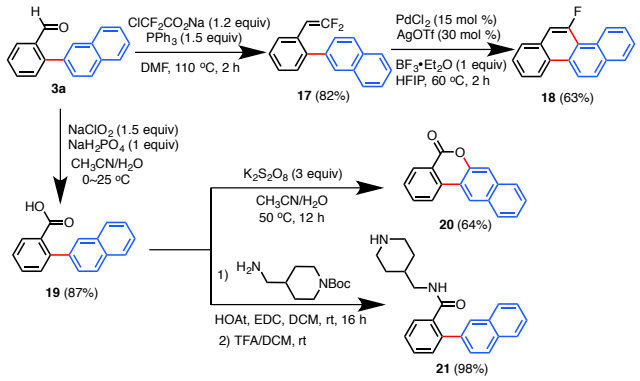
The aldehyde group in biaryl compounds can be easily modified and converted into a difluorovinyl scaffold, providing a strategy to prepare organic semiconducting material-relevant 5-fluorochrysene (**18**) by a subsequent annulation (Scheme 6). The oxidation of aldehyde functionality to carboxyl enables the formation of naphthylated benzoic acid (**19**). By the annulation and amidation of the carboxyl group, both 5*H*-dibenzo[*c*,*g*]chromen-5-one (**20**), which is of interest for material science, and biologically active muscarinic ace-

Scheme 5. Cr-Catalyzed Sequential Reductive and Oxidative Couplings of Unactivated C(aryl)–N/C(aryl)–H Bonds for the Synthesis of 2,6-Disubstituted Benzaldehydes[a]



[a]The sequential transformations of *ortho*-C(aryl)–N and C(aryl)–H bonds by Cr-catalyzed couplings were performed on a 0.2 mmol scale of **1**. Total yields are given.

Scheme 6. Applications in the Preparation of Material- and Medicinally Relevant Compounds



tylcholine receptor agonist **21** were prepared.[21]

3. CONCLUSIONS

In summary, we have developed a reductive cross-coupling between unactivated C(aryl)–N and C(aryl)–O bonds through ligand-enabled Cr catalysis. This reaction was accomplished by using the low-cost $CrCl_2$ as precatalyst, accompanied by dtbpy as an effective ligand and magnesium as a reductant. The approach enables the cross-electrophile coupling between two chemically inert and different bonds to form C–C bonds under mild conditions. Further mechanistic studies involving the isolation and characterization of reactive intermediates are ongoing.

4. EXPERIMENTAL SECTION

General Procedure for Cr-Catalyzed Reductive Cross-Coupling between Unactivated C(aryl)–N and C(aryl)–O Bonds. In a dried Schlenk tube were placed magnesium (19 mg, 0.8 mmol) and $CrCl_2$ (3 mg, 0.02 mmol). The tube was heated to around 400 °C under vacuum for 5 min using a heat gun. After cooling to room temperature, a mixture of dtbpy (5 mg, 0.02 mmol), the corresponding aniline **1** (0.2 mmol) and aryl ester **2** (0.8 mmol) in dry THF solution (2 mL) was added and stirred at 40 °C for 48 h. The mixture was then treated with a solution of aqueous HCl (3 N, 2 mL) and stirred at room temperature for 0.5 h. After neutralization with saturated aqueous solution of $NaHCO_3$, the mixture was extracted three times with ethyl acetate. The organic phases were collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired cross-coupling product **3**.

General Procedure for Cr-Catalyzed Sequential Transformations of Unactivated C(aryl)–N and C(aryl)–H Bonds. According to the procedure of Cr-catalyzed reductive cross-coupling of C(aryl)–N/C(aryl)–O bonds, the related *ortho*-aryl benzaldehyde **3** was obtained. Which was treated with benzylic amine (0.3 mmol, 1.5 equiv) in methanol (2 mL) in reflux for 6 h. After removal of the volatiles under vacuum, $CrCl_2$ (0.02 mmol), DCP (40 μL) and THF (2 mL) were added under atmosphere of nitrogen. After the mixture was stirred at room temperature for 5 min, Grignard reagent (0.4 mmol, 1.0 M in THF) was added dropwise by a syringe, and stirred at 40 °C for 12 h. The reaction was then quenched with aqueous HCl (3 M, 2 mL) and stirred for another 0.5 h. After neutralization by K_2CO_3, the organic phase was extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography to give the related disubstituted benzaldehyde **16**.

ASSOCIATED CONTENT

Supporting Information. Detailed optimization data; experimental procedures; characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org."

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Author Contributions

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Notes

The authors declare no competing financial interests.

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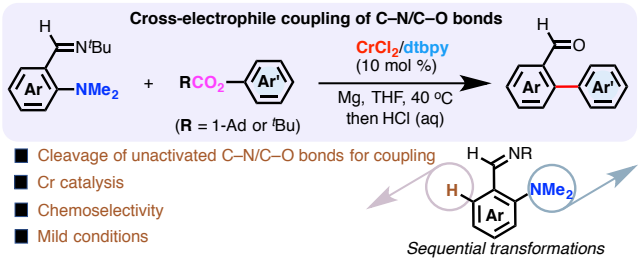
Cross-electrophile coupling of C–N/C–O bonds
H
N^{t}Bu
Ar
NMe$_2$
+
RCO$_2$
Ar^1
(R = 1-Ad or ^{t}Bu)
CrCl$_2$/dtbpy
(10 mol %)
Mg, THF, 40 °C
then HCl (aq)
H
O
Ar
Ar^1
Cleavage of unactivated C–N/C–O bonds for coupling
Cr catalysis
Chemoselectivity
Mild conditions
H
NR
H
Ar
NMe$_2$
Sequential transformations