

Nickel-catalyzed Ullmann-type Coupling Reaction to Prepare Tetra-*ortho*-substituted Biaryls

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Abstract: A nickel-catalyzed Ullmann-type reaction on the coupling of bis-*ortho*-substituted arylhalides to prepare tetra-*ortho*-biaryls was brought about in moderate to high yields. Bu_4NI might function as an efficient bridging ligand to accelerate the formation of dinickel-center intermediate, which subsequently eliminates to desired coupling product.

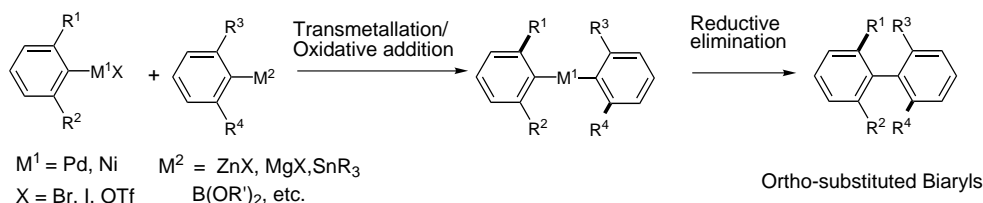
Key words: nickel, Ullmann-type reaction, tetra-*ortho*-substituted biaryls, bridging ligand

Biaryls are common structure motifs in natural products and are the core for many of the most effective chiral ligands.³ The synthesis of this class of compound has been effected by a number of useful methods⁴ (Scheme 1), albeit mostly using Cu-mediated methodology. Pioneering work by Semmelhack⁵ has shown that nickel-promoted Ullmann-type reaction was an efficient method for preparing biaryls bearing some sensitive functional groups. But, unfortunately, the combination of sterically hindered substrates to give products with four *ortho* substituents could not be accomplished using a nickel catalyst system.^{5,6}

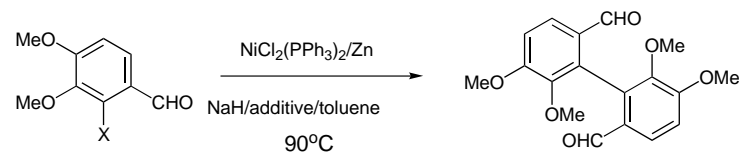
Many works indicated⁷ that polar solvents facilitate the solvation of nickel(II) complexes formed in the oxidative addition steps and thus promote the coupling process, and meanwhile the aryl radicals generated in the reaction tend to abstract hydrogen from the conventionally reported polar solvents (such as THF and DMF) and thus result in hydrogenolysis product of the aryl halides. It is therefore often hard to offer satisfactory yield while running such reaction in a polar solvent. Recently, we accomplished the coupling of arylhalides in toluene, using an in situ generated nickel catalyst.⁸ Toluene was found to considerably retard the dehalogenated process of the substrate. Here we

report the nickel-catalyzed Ullmann-type reaction of bis-*ortho*-substituted arylhalides in the presence of Bu_4NI . To our knowledge, this is the first example of a catalytic nickel-mediated Ullmann-type reaction to prepare tetra-*ortho*-substituted biaryls.

To establish an efficient protocol for coupling of bis-*ortho*-substituted arylhalides, we first tested the effect of Bu_4NI ⁹ in the coupling reaction of arylbromide **1a** and aryl iodide **1b** (Table 1). The ratio of *cp/rp* reversed from 36: 64 to 65: 35 in favor of the formation of the coupling product (*cp*, **2a**) (entry 1 vs 2) when 0.6 equiv of Bu_4NI was present in the reaction mixture. An increase of Bu_4NI from 0.6 equiv to 2 equiv caused an elevation in the ratio of *cp/rp* (entry 3 vs 2). Although the iodide ion was speculated as a ligand which could coordinate to the nickel center,^{7k} the yield of **2a** dropped when the amount of PPh_3 was decreased from 0.4 equiv to 0.2 equiv (entry 4 vs 3). This implies that PPh_3 is a stronger ligand than the iodide ion. Interestingly, 0.1 equiv of Bu_4NI was effective enough to obtain **2a** in moderate yield (entry 5). It was proposed⁸ that hydride from NaH might coordinate to the nickel center to form nickel-hydride which would eliminate to give reductive product (*rp*). Here it was also found that the ratio of *cp/rp* was slightly increased by using only 3.0 equiv of NaH (entry 6 vs 5). Zinc functions as a promoter^{8,10} (entry 6 vs 7). 0.2 equiv of nickel catalyst was necessary for coupling of arylbromide **1a** (entry 8 vs 7). Although previously⁷ it has been proposed that the halogen-exchanged reaction would be the initial step when Bu_4NI was added into the reaction mixture, the very low solubility of Bu_4NI in nonpolar solvents¹¹ (such as benzene, toluene) implies that this process might be very difficult. In entries 10 and 11, the ratio of *cp/rp* of aryl iodide **1b** was considerably increased in the presence of Bu_4NI .



Scheme 1 Transition metal-catalyzed coupling reaction to prepare biaryls

Table 1 Effect of Bu₄Ni in Nickel-catalyzed Ullmann-type Reaction on Substrate **1a** (X = Br) or **1b** (X = I)^a

Entry	NiCl ₂ (PPh ₃) ₂ (equiv)	PPh ₃ (equiv)	Zn (equiv)	NaH (equiv)	Bu ₄ Ni (equiv)	Reaction time (h)	Yield (%) ^b (isolated)	Ratio (<i>cp</i> : <i>rp</i>) ^c
1	0.2	0.4	3	6	–	12	95 (27)	36: 64
2	0.2	0.4	3	6	0.6	6	93	65: 35
3	0.2	0.4	3	6	2	4.5	94 (70)	80: 20
4	0.2	0.2	3	6	2	5	95	56: 44
5	0.2	0.4	3	6	0.1	3	96	65: 35
6	0.2	0.4	3	3	0.1	3	>95	70: 30
7	0.2	0.4	1	3	0.1	12	85	63: 37
8	0.1	0.2	3	3	0.1	7	>95	32: 68
9 ^d	0.2	0.4	3	3	–	4	>95 (53)	67: 33
10 ^d	0.2	0.4	3	3	0.1	1 ^e	>95 (73)	84: 16
11 ^d	0.1	0.2	3	3	0.1	1 ^e	>95 (75)	83: 17

^a All of the reactions were performed at 90–95 °C in toluene (0.2 M).

^b The total yields of coupling product (*cp*) and reductive product (*rp*) were determined by HPLC (in parenthesis they are the isolated yields of coupling product **2a**).

^c The ratios of coupling product (*cp*) to reductive product (*rp*) were determined by HPLC.

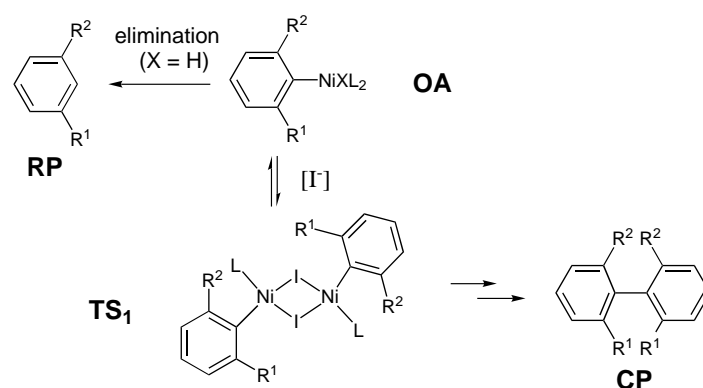
^d The substrate is aryl iodides (**1b**).

^e The reaction was ready in 1 hour (determined by TLC).

A proposed mechanism⁸ is shown in Scheme 2. It was observed that ratio of *cp*/*rp* at initial time was lower than that at the end of the reaction. Initial formation of mononickel complex **OA** might lead to coordination by the iodide ion as bridging ligand to form di-nickel complex **TS₁** as shown in Scheme 2. The former would favor the formation of the reductive product (**RP**) through a radical

mechanism^{7c} or the elimination of a nickel-hydride complex.^{8,13} However, the latter complex **TS₁** would form a di-arylnickel complex after ligand transfer and this would lead to coupling product (**CP**) by elimination.

With the optimized set of conditions (Table 1, entry 6 and entry 11) a range of arylhalides **1c–1**¹⁴ were examined (Table 2). Most yields of coupling products were dramat-

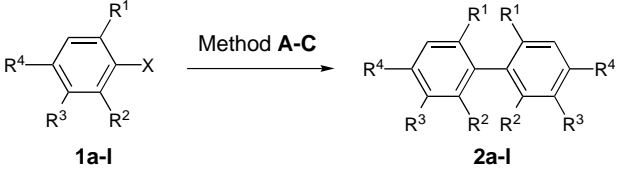


RP: reductive product; **OA**: oxidative addition;
TS₁: dinickel-center intermediate; **CP**: coupling product

Scheme 2 Proposed Mechanism for the Effect of Bu₄Ni in the Nickel-catalyzed Ullmann-type Coupling Reaction

ically increased in the presence of Bu_4NI . For example, the isolated yield for the coupling of **1d** was 77%, while it was only 44% in the absence of Bu_4NI (entry 4). The coupling product of **1c/1d** (entries 3 and 4) is a key intermediate for the synthesis of natural product, schizandrin.¹⁵ In the presence of 0.5 equiv of Bu_4NI , the coupling yields of **1k** and **1l** were increased to 72% and 45%, respectively (entries 11 and 12). The latter coupling product **2l** had been previously synthesized through a multi-step process.¹⁴ⁱ We have developed a mild and efficient method for preparing this compound. For the coupling of **1g**,¹⁴ some Cu-mediated methods^{14d,f} had previously been carried out in moderate yields under harsh conditions, however, the coupling product **2g** was afforded in 97% yield under our conditions (entry 7). The presence of a methyl ester functionality on one of the *ortho*-positions gave lower yields than an aldehyde group on the same position (entry 8 vs 1, entry 9 vs 2). This is probably caused by the greater bulkiness and the electronic effect of the methyl ester group. The rate of coupling of **1j** was very fast, however, it necessitated 30 mol% of catalyst (Method C, Table 2) because of the decomposition of the catalyst (entry 10).

Table 2 Nickel- Bu_4NI system catalyzed Ullmann-type reaction to prepare 2,2',6,6'-substituted Biaryls^a



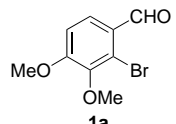
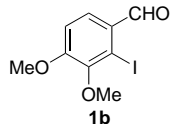
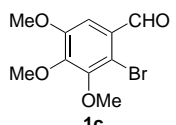
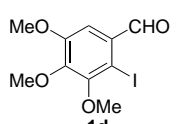
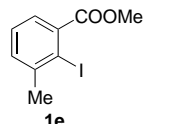
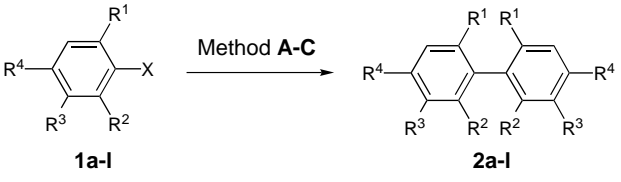
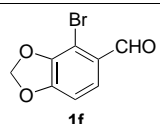
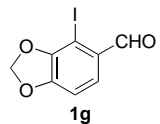
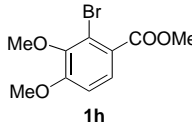
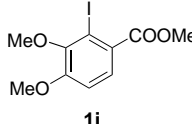
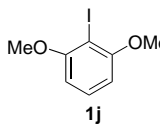
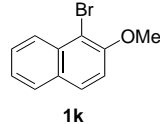
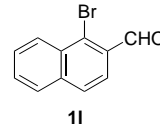
Entry	Substrate	Method	Time (h)	Yield% ^b (isol.)	Yield% ^c
1		A	3	70 (62)	27
2		B	1	83 (75)	51
3		A	6	78 (71)	30
4		B	2	82 (77)	44
5		B	1.5	93 (85)	65

Table 2 Nickel- Bu_4NI system catalyzed Ullmann-type reaction to prepare 2,2',6,6'-substituted Biaryls^a (continued)



Entry	Substrate	Method	Time (h)	Yield% ^b (isol.)	Yield% ^c
6		A	5	94 (89)	58
7		B	1.5	>99 (97)	91
8		A	8	33 (23)	3
9		B	1	68 (60)	29
10		C	1	80 (71)	30
11		A	4	83 (72)	52
12		A	7	55 (45)	18

^a Unless indicated, all of the reactions were performed with Zn (3 equiv), NaH (3 equiv), Bu_4NI (0.1 equiv) at 90 °C in toluene (0.2 M) (in parenthesis are the isolated yields of coupling product). Method A: $\text{NiCl}_2(\text{PPh}_3)_2$ (0.2 equiv)/ PPh_3 (0.4 equiv). Method B: $\text{NiCl}_2(\text{PPh}_3)_2$ (0.1 equiv)/ PPh_3 (0.2 equiv). Method C: $\text{NiCl}_2(\text{PPh}_3)_2$ (0.3 equiv)/ PPh_3 (0.6 equiv). The typical procedure is given in Ref. 16.

^b Determined by 300 MHz ^1H NMR spectra.

^c The isolated yields of coupling product were obtained without Bu_4NI .

In conclusion, this method represents a novel, efficient and mild synthesis of tetra-*ortho*-substituted biaryls through a nickel-catalyzed Ullmann-type coupling reaction using Bu_4NI as an additive. Iodide might act as a

bridging ligand to favor the formation of a diarylnickel complex and sequentially eliminate to give the desired biaryls. To our knowledge, it is the first example of a nickel-catalyzed reaction to obtain this kind of highly hindered biaryls. This reaction is synthetically useful as well as mechanistically intriguing.

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References and Notes

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- (15) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.
- (16) **Typical procedure** (Method B): A 20 mL schlenk flask was charged with $\text{NiCl}_2(\text{PPh}_3)_2$ (0.1 mmol), PPh_3 (0.2 mmol), Zn dust (3.0 mmol), NaH (3.0 mmol, oil-free), Bu_4NI (0.1 mmol) and arylhalide **1g** (276 mg, 1.0 mmol), sealed with a rubber septum, evacuated and filled with argon several times (vacuum line). Freshly distilled toluene (5 mL) was added via a syringe. The mixture was stirred at 90 °C for 1.5 h, then cooled and quenched by 5% HCl(aq). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were washed with 5% NaHCO_3 (aq), brine and dried over Na_2SO_4 . Upon removal of the solvent, the corresponding biaryl **2g** was obtained as a white solid (144 mg, 0.483 mmol) in 97% yield after flash chromatography on silica gel (EtOAc-PE, 1: 3). ^1H NMR spectral data of **2g** is in agreement with published data (ref. 12d and 12f). Other coupling products (**2a**, **c-l**) are in agreement with results reported in literature (ref.12).