A New Reagent System for Modified Ullmann-Type Coupling Reactions: NiCl₂(PPh₃)₂/PPh₃/Zn/NaH/Toluene

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Introduction

Compared with the classical Cu-mediated¹ Ullmann reaction, other transition metal (such as Pd and Ni)catalyzed²⁻⁵ coupling reactions are generally milder and more efficient, tolerate a large variety of functional groups, and may furnish biaryls in excellent yields. However, the homocoupling reactions promoted by these transition metals are sensitive to the substrates bearing free OH groups and bisortho substitutents.⁶ It is noticed²⁻⁵ 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 radicals⁷ 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. During the course of the total synthesis of bibenzopyran-4-ol (1), a natural product isolated⁸ from the root of *Aloe barbadensis*, we found a new reagent system for coupling arylhalides and vinylhalides. Herein, we wish to report some unprecedented results.

Results and Discussion

In an attempt to prepare compound A (a potential precursor to 1) by homocoupling of 3-iodo-6-methoxyben-

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(6) Knight, D. W. In *Comprehensive Organic Chemistry*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, p 499. The Ullmann-type coupling reactions of those haloarenes with carboxlic acids were not successful under Caubere's NiCRA^{11c} or Ni(COD)₂ developed by Semmelhack's group with the fashion of carboxylate salts.

zopyran-4-one (2), it was observed that the isolated yield of A using NiCl₂(PPh₃)₂/PPh₃/Zn in DMF was elevated when K_2CO_3 was present as a base in the reaction mixture, while employing Cu¹ (either with DMF, PhNO₂, or pyridine as solvent) or Ni(0) as catalyst under the standard conditions,^{4b} the isolated yield of A was normally less than 15%. In addition, the ratio of A/B was



Bisbenzopyran-4-ol (1)

improved toward more of the former (Table 1, entries 1 and 2), although **B** was still formed as major product. In polar solvents, arylnickel neutral species can be protonated or abstract hydrogen from the solvent to form cationic hydrides.⁹ The Brönsted acidity of nickel hydride intermediate [ArNiLnH]⁺ requires the powerful base (such as NaH, LiH) to remove the proton, and the reductive elimination process can thus be retarded.^{3b}

To find a better scavenger for the acidic proton,⁹ several bases and solvents were examined (Table 1). It shows that if large excess of sodium hydride was present in the reaction system, the ratio of A/B reversed from 40:60 to 80:20 in favor of the formation of the coupling product A (entries 3 vs 2). An increase of NaH from 10 equiv to 20 equiv caused a drop in the ratio of **A**/**B** (entries 4 vs 3). Replacement of DMF with THF had no practical effects (entries 5 vs 3). In addition, the reaction did not occur when NaH was utilized as sole reductant in THF. Therefore, NaH functioned as a base in polar solvent in the absence of other additives.¹¹ When benzene was employed as the reaction media, the yield of coupling product increased dramatically (up to 91.9%, entry 6). Even better selectivities (97.8% and >99%) were observed when toluene was used as the solvent (entries 7 and 8, respectively). The catalyst loading affected the selectivity, possibly due to the hydrogenolysis of substrates by the nickel hydride species.^{11,12} On the other hand, the results from the presence of NaO^tBu or NaBH₄ were not encouraging (entries 9 and 10), and compound **D** was obtained as the major undesired product in the Ni(0)-NaO^tBu system (entry 9).

To the best of our knowledge, the combination of metal Zn and NaH in toluene as the reductive system has never been reported, even though each of them acts as a good reductant in polar solvents.^{4b,12} Further scrutiny with the same reaction shown in Table 1 revealed that (Table 2): (a) higher temperature accelerated coupling reaction (entries 1 vs 2, 3 vs 4, 7 vs 8); (b) the presence of excess

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Table 1. Results of Modified Ni(0)-Catalyzed Homocoupling of Compound 2a



^a The reactions were performed using 1 equiv of NiCl₂(PPh₃)₂, 2 equiv of PPh₃, 4 equiv of Zn, and 8 equiv of additive except entry 8, in which 0.5 equiv of nickel catalyst was used. ^b 20 equiv of NaH was used. ^c In this entry, **D**, as an intermediate for the synthesis of benzopyranone (see ref 10), was the major side product through the hydrolysis of compound **B**.

entry	PPh ₃ (2 equiv)	Zn (4 equiv)	NaH (8 equiv)	<i>T</i> (°C)	time (h)	convn (%)	yield (%)	ratio (A/B) ^b
1	+	+	+	90	6	100	97	97 8.9 9
2	+	+	+	rt	21	<10	97	20:80
$\tilde{3}$	+		+	90	18	100	99	90:10
4	+		+	rt	24	49	99	94:6
5		+	+	90	24	59	97	81:19
6		+	+	rt	3	82 ^c	99	47:53 ^c
						95^d	95	$40:60^{d}$
7			+	90	24	66.5	99	44:56
8			+	rt	24	40	98	82:18
9	+	+		90	6		e	

Table 2.	Varieties	of Reaction	Conditions	(in Toluer	ne)ª
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^a All reactions were run using 1 equiv of NiCl₂(PPh₃)₂ in toluene at rt or 90 °C. "+" represents this component being present in the reaction mixture. For example, in entry 1, the ratio of NiCl₂(PPh₃)z/PPh₃/Zn/NaH/substrate is 1:2:4:8:1. ^b The yields and the ratios were determined by HPLC. ^c Determined by HPLC. ^d Traces of the substrate were detected. The yield and the ratio were determined by 1H NMR (300 MHz). ^e No products were detected.

ligand PPh_3 favored the formation of coupling product ${\bf A}$ (entries 1 vs 5, 3 vs 7, 4 vs 8); and (c) the reaction was accelerated in the presence of metallic Zn (entries 1 vs 3, 6 vs 8). Although the function of Zn dust is still unclear,¹³ all of the components are necessary for our new reagent system to obtain the current excellent results.

Several different mechanisms have been proposed in the literature^{4b,7a,11c,14-16} for the nickel(0)-catalyzed homocoupling reactions of arylhalides. As no dibenzyl was found among the reaction products (monitored by GC-MS), a free radical mechanism⁶ can be ruled out. We presume a different potential mechanism as shown in Scheme 1. Under our conditions, compound E was formed simultaneously with C (Table 1, entries 4 and 5), and because **C** and **E** are not obtained from the hydrogenation of A and B, respectively, thus, the formation of C and E

Proposed Mechanism for the Scheme 1. Formation of C and E in a Polar Solvent



might be from the same intermediate, such as $3^{16c,17,18}$ in Scheme 1. In addition, increasing the content of THF in toluene to 20% led to the formation of C and E;

⁽¹³⁾ Some unpublished results show that the ratio of coupling product to reductive product is dependent on the ratio of Zn dust to nickel catalyst. The function of zinc may be reminiscent of the reported hypothesis.

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(15) A hypothesis explained that the nickelate intermediate could form a bridged Zn complex (heteronuclear complex) on the zinc surface and facilitate electron-transfer reaction. This process might occur in polar solvents such as DMAc; see ref 4b.

⁽¹⁶⁾ There are established examples of hydride and aryl groups as bridging ligands. The transition state (or intermediate) for such an inner-sphere electron transfer process can be depicted as singly bridged or doubly bridged; see: (a) Basolo, F.; Pearson, R. G. *Mechanisms of Inorganic Reactions*; Wiley: New York, 1967; pp 482. (b) Wilkins, R. G. Kinetics and Mechanisms of Transition Metal Complexes; Allyn and Bacon: Boston, 1974. (c) Yamamoto, Y.; Wakabayashi, S.; Osakada, K. *J. Organomet. Chem.* **1992**, *428*, 223. (d) Kristjánsdóttir, S. S.; Norton, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 4366 and references therein. (17) For a σ -phenylpalladium hydride species, see: Grushin, V. V.;

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) Seq Ni catalyst			
R-X (X = Br, I) -		R-R +	R-H	
4a-k		5a-k	6	
substrates	product 5 (yield %)	ratio (5:6)	yield % (lit.) ^b	
N Br 4a	5a (93)	>95 : 5	72 (5f)	
Me 4b	5b (95)	>95 : 5	-	
	5c (93)	>95 : 5	_	
R				
4 d R=H	5d (96)	100:0	-	
4e R=OTBDPS	5e (92)	100:0	_	
Ph R ₂				
4f R_1 =Br, R_2 =H	5f (75)	>95 : 5 b	70 (16)	
4g R ₁ =H, R ₂ =Br	5g (30)	с	<5 (17)	
COOH I 4h	5h (70)	с	0 (10c)	
HOOC-	5i (60)	с	70 (20b)	
COOMe I Me 4j	5j (65)	с	-	
Br OMe 4k	5k (52)	с	_	

Table 3.	Homocoupling of Some Substrates under	Гhis
	Condition ^a	

^a All reactions were run using 0.5 equiv of nickel catalyst. ^b Different methods were reported in the literature, like as Ni(PPh₃)₄/DMF, Ni(COD)₂/DMF, and "NiCRA". ^c TLC detected a trace of reductive product.

therefore, the two hydrogen atoms added to C may be taken from NaH and the polar solvent, respectively. Compound **B** can also be formed through the reductive elimination of the mononickel complex [ArNiHL₂].

To explore the scope and limitations of this coupling conditions, reactions of haloarene **4a**, α -iodo- α , β -unsaturated ketones 4b-e, haloalkenes 4f,g, halobenzoic acid **4h**,**i**, and bisortho-substituted halobenzene **4j**,**k** were investigated (Table 3). Most of them could be coupled smoothly in high yields with excellent selectivities. In the

case of 4f, no envne and divne products were observed.¹⁹ Although the coupling yield and selectivity of β -bromostyrene 4g were moderate, the coupling product could not be detected in the absence of NaH.^{20a}

It was generally considered that the limitations associated with nickel-based approaches are the free hydroxyl groups (such as OH, COOH) and the steric effects of ortho substitutents, especially bisortho substitutents.^{3b,6,11c} Under our conditions, halobenzoic acids 4h,i and bisortho-substituted halobenzenes 4j,k could also be coupled successfully with good yields. The homocoupling of these three kinds of substrates were hardly successful under other reported Ni-catalyzed Ullmann-type coupling conditions.^{3b,6,11c,18,22} It is difficult for aryl halide bearing bisortho-substitutents to add oxidatively to the ArNi(I)- L_3 to give an Ar₂Ni(III) L_2 complex.⁶ The formed 2,2',6,6'tetrasubstituted biaryls are prone to the dinickel hydride intermediates.

In summary, we have developed a powerful coupling system involving Zn and NaH for nickel(0)-catalyzed Ullmann-type reactions, especially for bisortho-substituted halobenzenes and halobenzoic acids. It is the first time the nickel-modified Ullmann-type reaction has been performed in a nonpolar solvent while the catalyst is generated in situ. As demonstrated in the text, the nonpolar solvent and the hydride as bridging ligand may play a significant role. Current work in our laboratory is focused on the further elucidation of the mechanism as well as the scope of this new reagent system.

Experimental Section

General Methods. Toluene was freshly distilled from sodiumbenzophenone ketyl. Zn dust²² was activated according to the literature. NiCl₂(PPh₃)₂,²³ 4d,²⁴ 4e,²⁴ 4j,²⁵ and 4k²⁶ were prepared by literature procedures. NaH was washed twice with dry hexane under N₂. ¹H NMR (300 MHz) spectra were recorded in CDCl₃, and chemical shifts are given in Hz. Column chromatography was performed with 300-400 mesh silica gel using flash column techniques. Elemental analyses were performed by EA-MOD 7106. Low-resolution mass spectra were recorded on a Finigan-4201 spectrometer, IR on FTS-185. The melting points were not corrected. ¹H NMR spectral data of 5a,²⁷ 5b,²⁸ $\mathbf{5c}$, 28 5f, 16 5g, 17 5h, 27 5i, 27 5j, 25 and $\mathbf{5k}^{29}$ are in agreement with published data.

General Procedure. The Schlenk flask was charged with NiCl₂(PPh₃)₂ (0.5 mmol), PPh₃ (1 mmol), Zn dust (3 mmol), NaH (8 mmol, oil-free), and aryl halide (1 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 70-90 °C for 2-6 h, cooled, and then quenched with 5% HCl (aq). The organic layer was extracted

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(21) When a simple aryl halide, p-OMeC₆H₄I, was treated, the yield of coupling product was 47% and the major side product was $p\text{-}OMeC_6H_4Ph$ (35%).

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with CHCl₃ and dried over Na₂SO₄. Upon removal of of the solvent, the corresponding biaryl was obtained after flash chromatography on silica gel (CH₂Cl₂/EtOAc) and recrystallization from CH₂Cl₂/MeOH.

3,3'-**Bis(6-methoxychromone)** (A): mp 257–258 °C; MS 350 (M⁺), 349 (M + H), 348, 335, 322, 307; FT-IR (cm⁻¹) 3080, 2976, 1645, 1567, 1484, 1313, 1150, 870, 817, 788, 711; ¹H NMR (CDCl₃, 300 MHz) δ 8.86 (s, 2H, H-2), 7.65 (d, J = 3.0 Hz, 2H, H-5), 7.47 (d, J = 9.2 Hz, 2H, H-7), 7.30 (dd, J = 9.2, 3.0 Hz, H-8), 3.92 (s, 6H, OCH₃). Anal. Calcd for C₂₀H₁₄O₆: C, 68.57; H, 4.03. Found: C, 68.58; H, 3.98.

3 • (6 • Methoxychromone • 3) • 6 • methoxy • 2, 3 • 2 *H*chromone (C): mp 205–206 °C; MS 352 (M⁺), 351 (M – H), 335 (M – 15), 321, 201, 150; FT-IR (cm⁻¹) 2925, 1683, 1640, 1590, 1494, 1165, 843, 826, 796, 744; ¹H NMR (CDCl₃, 300 MHz) δ = 7.87 (s, 1H, H-2), 7.56 (d, *J* = 3.0 Hz, 1H, H-5), 7.42 (d, *J* = 3.0 Hz, 1H, H-5), 7.41 (d, *J* = 9.0 Hz, 1H, H-8), 7.28 (dd, *J* = 9.0, 3.0 Hz, 1H, H-7), 7.14 (dd, *J* = 9.0, 3.0 Hz, 1H, H-7), 6.96 (d, *J* = 9.0 Hz, 1H, H-8), 4.69 (t, *J* = 11.4 Hz, 1H, H-3), 4.56 (dd, *J* = 11.4, 5.3 Hz, 1H, H-2), 4.21 (dd, *J* = 11.4, 5.3 Hz, 1H, H-2), 3.88, 3.82 (each s, 6H, 2 × OCH₃). Anal. Calcd for C₂₀H₁₆O₆: C, 68.18; H, 4.58. Found: C, 68.40; H, 4.47.

Preparation of 3-Iodo-6-methoxychromone (2). To a stirred suspension of powered sodium (2.38 g, 103 mmol) in dry ether (60 mL) was added dropwise a well-cooled solution of 2'methoxy-5'-hydroxyacetophenone (4.08 g, 24.6 mmol) in freshly distilled ethylformate (8 mL, 100 mmol) and dry ether (200 mL). The reaction mixture was stirred for 4 h in an ice bath and then overnight at rt. Twenty millilters of ethylformate-ether mixture (1:10) was added, and the reaction mixture was refluxed for 1 h. On cooling, water (100 mL) was added carefully, and the alkaline layer was separated. The alkaline layer was acidified by 50% H_2SO_4 (pH < 1) and refluxed for 1 h. It was cooled and extracted with $ilde{C}HCl_3$ (30 mL imes 3). The combined organic layers were washed with brine and dried over Na₂SO₄. 5-Methoxychromone was obtained as yellowish solid after the solvent was evaporated. The crude product 5-methoxychromone and piperidine (6.2 mL, 62.5 mmol) were refluxed in methanol (50 mL) for 3 h. Rotary evaporation gave a yellow solid, which was dissolved in CHCl₃ (40 mL). Pyridine (2 mL, 25 mmol) and iodide (12.7 g, 50 mmol) were added into the solution in one portion. The reaction mixture was stirred overnight and quenched with 15 mL of saturated Na₂S₂O₃ (aq). After the mixture was vigorously stirred at room temperature over 30 min, the organic layer was separated. The water layer was extracted with CHCl₃ (30 mL \times 3). The combined organic layers were washed with brine and dried over Na₂SO₄. The white solid (6.83 g, 22.6 mmol) was obtained in 92% yield after flash column chromatography on silica gel (CH2Cl2/ĚtOAc 85/15).

3-Iodo-6-methoxychromone (2): mp 118–119 °C; MS 302 (M⁺), 303 (M + H), 287, 272, 119, 107, 79; FT-IR (cm⁻¹) 3072, 1653, 1616, 1565, 867, 823, 715, 566, 479; ¹H NMR (CDCl₃, 300 MHz) δ 8.29 (s, 1H, H-2), 7.58 (d, J = 3.0 Hz, 1H, H-5), 7.41 (d, J = 9.2 Hz, 1H, H-8), 7.29 (dd, J = 9.0, 3.0 Hz, 1H, H-7), 3.91 (s, 3H, OCH₃). Anal. Calcd for C₂₀H₁₄O₆: C, 39.76; H, 2.34; I, 42.01. Found: C, 39.76; H, 2.27; I, 42.09.

3-Iodo-6-methylchromone (4b): mp 129–131 °C; MS 286 (M⁺), 258, 159, 103; FT-IR (cm⁻¹) 1644, 1614, 1598, 1558, 1482, 867, 817, 778, 543, 472; ¹H NMR (CDCl₃, 300 MHz) δ 8.28 (s, 1H, H-2), 8.03 (d, J = 2.0 Hz, 1H, H-5), 7.52 (dd, J = 8.3, 2.0 Hz, 1H, H-7), 7.37 (d, J = 8.3 Hz, 1H, H-8), 2.47 (s, 3H, CH₃). Anal. Calcd for C₁₀H₇IO₂: C, 41.97; H, 2.47; I, 44.38. Found: C, 42.03; H, 2.41; I, 44.48.

3-Iodo-chromone (4c): mp 95–96 °C; MS 272 (M⁺), 244, 145, 89; FT-IR (cm⁻¹) 1646, 1609, 1597, 1556, 868, 833, 765, 540, 514; ¹H NMR (CDCl₃, 300 MHz): $\delta = 8.31$ (s, 1H, H-2), 8.25 (dd, J = 8.5, 1.4 Hz, 1H, H-5), 7.72 (td, J = 8.5, 1.4 Hz, 1H, H-7), 7.27–7.50 (m, 2H, H-6, 8). Anal. Calcd for C₉H₆IO₂: C, 39.71; H, 1.84; I, 46.69. Found: C, 39.76; H, 1.84; I, 46.31.

2,2'-Bis(2-cyclohexen-1-one) (**5d)**: mp 109–110 °C; MS 302 (M⁺), 303 (M + H), 287, 272, 119, 107, 79; FT-IR (cm⁻¹) 3072, 1653, 1616, 1565, 867, 823, 715, 566, 479; ¹H NMR (CDCl₃, 300 MHz) δ 8.29 (s, 1H, H-2), 7.58 (d, J = 3.0 Hz, 1H, H-5), 7.41 (d, J = 9.2 Hz, 1H, H-8), 7.29 (dd, J = 9.0, 3.0 Hz, 1H, H-7), 3.91 (s, 3H, OCH₃). Anal. Calcd for C₂₀H₁₄O₆: C, 39.76; H, 2.34; I, 42.01. Found: C, 39.76; H, 2.27; I, 42.09.

2,2'-Bis(4-*tert***-butyldiphenylsilyloxy-2-cyclohexen-1-one)** (5e): MS 698 (M⁺), 641, 563, 199, 135, 77; FT-IR (cm⁻¹) 2960, 2859, 1893, 1683, 1590, 1106; ¹H NMR (CDCl₃, 300 MHz) δ 7.69 (m, 8H, Ph), 7.35–7.49 (m, 12H, Ph), 6.61 (d, J = 2.4 Hz, 0.6 \times 2H, H_{3,3}), 6.57 (d, J = 1.6 Hz, 0.4 \times 2H, H_{3,3}), 4.51–4.58 (m, 2H, H_{4,4}), 2.48–2.55 (m, 2H, H_{6,6}), 2.16–2.28 (m, 2H, H_{6,6}), 2.05–2.08 (m, 4H, H_{5,5}), 1.09 (s, 18H).

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Supporting Information Available: ¹H NMR spectra for **A**, **C**, **2**, **4b**, **c**, and **5d**, **e** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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