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Nickel-Catalyzed Coupling of Aryl Iodides with Aromatic Aldehydes: Chemoselective Synthesis of Ketones

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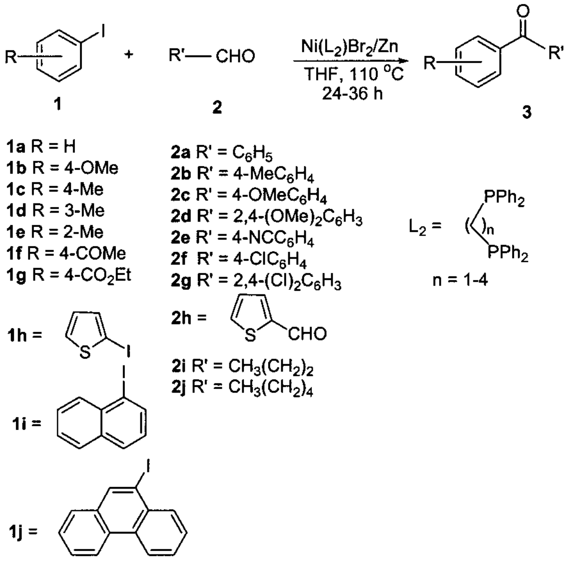
Abstract: Aryl iodides (ArI) couple with aryl aldehydes (Ar′CHO) in the presence of Ni(dppe)Br_2 and Zn to give the corresponding biaryl ketones (ArCOAr′). The use of a bidentate phosphine complex is critical to the success of this catalytic reaction. The reaction provides a new procedure for the synthesis of various functionalized biaryl ketones.

The methods available for direct synthesis of ketones from alkyl or aryl halides are few and usually require a multistep process in classical organic synthesis. Most of these reactions involve the oxidation of the corresponding secondary alcohols using more than stoichiometric amount of chromium reagents as the oxidizing agent.[1] Aromatic ketones can be synthesized from Friedel−Crafts reaction via acylation in the presence of $AlCl_3$. This method provides ketones directly from aromatic hydrocarbons and has been known for many years.[2] The coupling of organometallic reagents with acyl chlorides using transition metals as catalysts usually provides ketones in high yields,[3,4] but anhydrous conditions should be maintained for both the reaction partners. Miyaura, Suzuki and coworkers reported a palladium-catalyzed synthesis of benzophenones or benzyl ketones via the cross-coupling of arylboronic acids with aryl halides, triflates, or benzyl halides under carbon monoxide atmosphere.[5] Reports for direct ketone synthesis from organic halide and aldehydes via activation of aldehyde hydrogen by transition metal catalysts are also available.[6a−b] However, these reactions are limited with respect to substrates and/or require more than stoichiometric amount of metal salts. Very recently, a rhodium(I)-catalyzed coupling of aryl iodides with N-pyrazyl aldimines to form the corresponding ketimines, which form ketones upon hydrolysis, was reported by Hartwig et al.[6c] The formation of ketones by this method requires two reaction steps and very high temperature.

Our ongoing interest in nickel-mediated carbon−carbon bond forming reactions[7] led us to explore the reactions of aryl halides with aldehydes. In this paper, we wish to report for the first time a nickel-catalyzed coupling of aryl iodides with aldehydes to give ketones in fair to good yields (eq 1). This convenient one-pot synthesis of ketones appears to involve both addition of aryl group to aldehydes and β-hydride elimination of the resulted alkoxide in the same reaction system.



Treatment of iodobenzene (**1a**) with benzaldehyde (**2a**) in the presence of Ni(dppe)Br_2 (10%) and Zn at 110 °C under N_2 in THF gave benzophenone (**3a**) in 84% yield. Under similar reaction conditions, bromobenzene afforded only a small amount of ketone **3a** (23%), the major product being diphenylcarbinol (67%). As our previous findings,[8] the catalytic reaction proceeds smoothly only with bidentate phosphine nickel complexes. Monodentate phosphine complexes are completely ineffective, whereas Ni(dppm)Br_2, Ni(dppe)Br_2, Ni(dppp)Br_2, and Ni(dppb)Br_2 afforded **3a** in 74, 84, 77, and 32% yields, respectively. Under similar conditions, palladium complexes Pd(dppe)$_2X_2$ (X = Cl and Br) gave no expected product at all. Solvent plays a crucial role in this catalytic reaction. THF is superior to other solvents. In low polarity solvent such as toluene the catalytic reaction did not occur at all. In acetonitrile or DMF several unknown side products along with benzyl alcohol, the reduction product of benzaldehyde, was observed. At refluxing temperature of THF the reaction gave a mixture of benzophenone and

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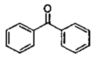
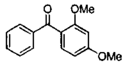
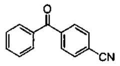
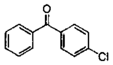
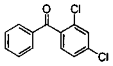
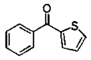
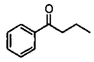
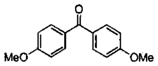
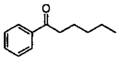
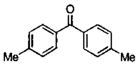
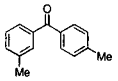
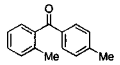
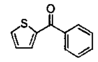
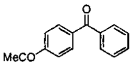
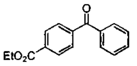
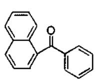
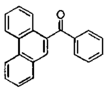
Table 1. Synthesis of Biaryl Ketones in the Presence of Ni(dppe)Br$_2$/Zn[a]

entry	1	2	product[b]	3	Time (h)	Yield (%)[c]
1	**1a**	**2a**		**3a**	30	84
2	**1a**	**2d**		**3b**	30	72
3	**1a**	**2e**		**3c**	30	57
4	**1a**	**2f**		**3d**	30	75
5	**1a**	**2g**		**3e**	30	66
6	**1a**	**2h**		**3f**	30	47
7	**1a**	**2i**		**3g**	36	33[d]
8	**1b**	**2c**		**3h**	24	87
9	**1a**	**2j**		**3i**	36	43[d]
10	**1c**	**2b**		**3j**	30	79
11	**1d**	**2b**		**3k**	30	69
12	**1e**	**2b**		**3l**	30	58
13	**1h**	**2a**		**3f**	36	34
14	**1f**	**2a**		**3m**	36	51
15	**1g**	**2a**		**3n**	36	53
16	**1i**	**2a**		**3o**	36	71
17	**1j**	**2a**		**3p**	36	63

[a] Reaction conditions: aryl iodide (1.25 mmol), aldehyde (1.00 mmol), Ni(dppe)Br$_2$ (0.100 mmol), Zn (2.75 mmol) in THF (4 mL) at 110 °C. [b] Satisfactory spectra of ^{1}H, ^{13}C NMR, and MS for each product were obtained. [c] Isolated yields; yields were based on aldehyde used. [d] Iodobenzene (1.00 mmol), aldehyde (1.50 mmol) were used and yields were based on iodobenzene.

diphenylcarbinol in a 73/27 ratio. However, at higher temperature (110 °C), benzophenone (**3a**) was formed exclusively.

This nickel-catalyzed ketone formation was successfully extended to a series of aldehydes and aryl iodides. The results of these studies are listed in Table 1. Most aryl iodides bearing either electron-rich or electron-withdrawing substituents reacted smoothly to give ketones in fair to good yields. However, aryl iodides with electron-withdrawing groups need longer reaction time, and the product yields are comparatively lower. This may be attributed to lower nucleophilicity of these aryl groups. The arylation of aliphatic aldehydes such as *n*-butyraldehyde and *n*-hexaldehyde was slower, and the corresponding yields are low probably because of the poorer electrophilicity of aliphatic aldehydes compared to aromatic aldehydes (entries 7, 9). The position of a substituent on aryl iodides also influences the yield of the reaciton. Ortho-substituted aryl iodides usually give lower yields than do meta- or para-substituted ones (entries 10–12).

As illustrated in Table 1, this methodology chemoselectively transforms a variety of aryl iodides and aldehydes into the corresponding ketones in the presence of functional groups that readily react with organolithiums or Grignard reagents (entries 3–5, 14, 15). Heterocyclic ketones can also be easily prepared by our method. Iodobenzene reacted smoothly with 2-thiophenecaboxaldehyde under similar reaction conditions to give phenyl-(2-thienyl)methanone (**3f**). Product **3f** can also be prepared alternatively by treating 2-iodothiophene with benzaldehyde (entry 13). In most of these reactions, small amounts of biaryls (3–11%) and pinacols (2–5%) were detected. For biaryl formation, electron-donating aryl iodides are slightly more favorable than electron-withdrawing ones. Biaryl formation is due to the homocoupling of aryl iodides [9] and pinacol formation is caused by the presence of ZnI$_2$ formed in situ in the reaction mixture.[10]

Based on the established nickel chemistry and foregoing results, we proposed the following mechanistic pathways (Scheme 1) to account for the present catalytic process. Reduction of Ni(II) to Ni(0) by zinc metal with the formation of zinc halide likely initiates the catalytic reaction. Oxidative addition of aryl iodides to Ni(0) generates organonickel(II) species **4**. Zinc halide (a Lewis acid) abstraction of an iodide from **4** forms a cationic nickel species **5**. Coordination of aldehyde affords a nickel intermediate with the aryl group cis to the coordinated aldehyde because of the bidentate chelating phosphine ligand. Migration of the aryl group to the carbonyl carbon of coordinated aldehyde affords a nickel alkoxide **6**. Subsequent β-hydride elimination gives the desired ketone and nickel hydride **7**. Reaction of HX generated from reductive elimination of **7** with Zn powder affords zinc halide with evolution of H$_2$.[11]

The formation of Ni(0) in the first step gains support from the fact that when Ni(dppe)Cl$_2$, Ni(dppe)Br$_2$ or Ni(dppe)I$_2$ is used, the presence of zinc powder is necessary to initiate the reaction. The proposed iodide dissociation is evidenced by the observation that a stoichiometric reaction of iodobenzene (**1a**) with benzaldehyde (**2a**) in

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(9) (a) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460. (b)Yamamoto, T.; Wakabayashi, S.; Osakada, K. *J. Organomet. Chem.* **1992**, *428*, 223.

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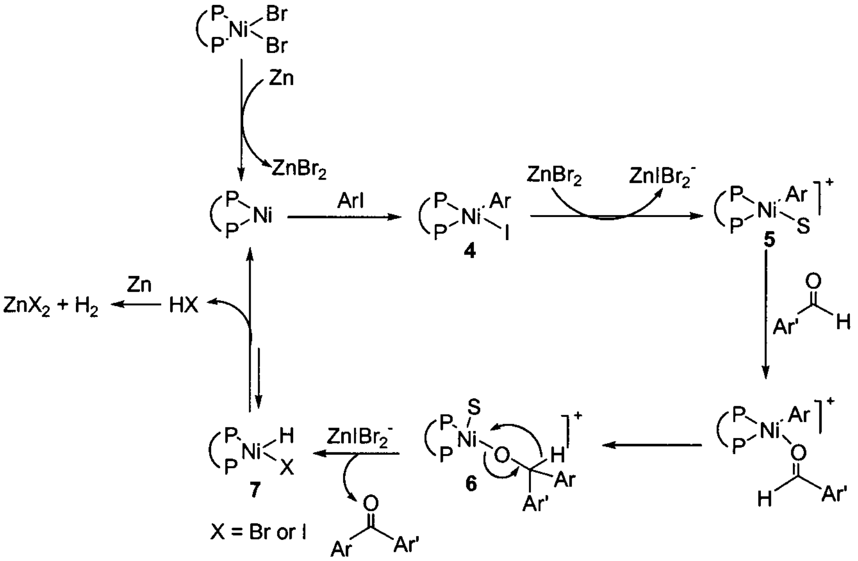
(11) **Detection of H$_2$**: To a sidearm flask were added Ni(dppe)Br$_2$ (0.10 mmol), Zn (2.75 mmol), iodobenzene (1.25 mmol), benzaldehyde (1.00 mmol), and THF (4.0 mL). The flask was flashed several times with N$_2$, and the N$_2$ gas was then partially evacuated. The sealed reaction flask was heated at 65 °C for 4 h. The flask was cooled to room temperature, and the inside gas was sampled by a pressure-lock syringe and was analyzed by a mass spectrometer (Finnigan MAT 95 XL). A sharp peak at mass number 2.0 confirms the presence of H$_2$.

Scheme 1



the presence of Ni(cod)$_2$/dppe (1:1) did not give any benzophenone (**3a**). However, the same reaction proceeds smoothly, giving 48% isolated yield of **3a** in the presence of 1 equiv of ZnI$_2$. The result strongly indicates that zinc halide abstracts an iodide from the nickel center and creates a vacant coordination site for the aldehyde. It should be noted here that although biaryl ketone was formed, no H$_2$ was detected. However, for the same reaction in the presence of Zn and ZnI$_2$, H$_2$ gas was evolved. Therefore, H$_2$ was formed only after reaction with Zn. For each ketone formed, the catalytic reaction produces a HI (or the equivalent) based on the stoichiometry (eq 1). It is likely that zinc metal acts as a proton scavenger by converting the acid produced into H$_2$ gas in the reaction.

In conclusion, we have demonstrated a highly chemoselective nickel-catalyzed coupling reaction of aryl iodides with aryl aldehydes to give the corresponding ketones in good yields. The simple experimental operation makes this catalytic reaction a convenient and straightforward route for the synthesis of ketones, in particular, of functionally substituted ketones. Attempt to extend the scope of our new procedure to the synthesis of more complex molecules is underway.

Experimental Section

Representative Procedure for the Coupling of Aryl Iodides with Aldehydes. Ni(dppe)Br$_2$ (0.062 g, 0.10 mmol) and Zn powder (0.180 g, 2.75 mmol) were placed in a screw-capped vial. The vial was flashed with N$_2$ and then sealed with septum. Iodobenzene (0.255 g, 1.25 mmol), 4-cyanobenzaldehyde (0.131 g, 1.00 mmol), and THF (4.0 mL) were added to the reaction mixture via syringe. The septum was removed, and the vial was sealed with the screw cap quickly under N$_2$. The system was heated at 110 °C with stirring for 30 h. The reaction mixture was cooled to room temperature, diluted with ether, filtered through a thin Celite pad, and washed with ether. The filtrate was concentrated, and the crude residue was purified through a silica gel column using hexane/EtOAc (V/V = 95/5) as eluent to give **3c** (0.119 g) in 57% yield. ^{1}H NMR (CDCl$_3$) δ 7.48 (t, 2 H, $J = 7.8$ Hz), 7.61 (t, 1 H, $J = 7.8$ Hz), 7.75 (d, 2 H, $J = 7.7$ Hz), 7.76 (d, 2 H, $J = 7.7$ Hz), 7.84 (d, 2 H, $J = 7.6$ Hz); ^{13}C NMR δ 115.53, 117.93, 128.54, 129.98, 130.15, 132.08, 133.24, 136.21, 141.11, 194.96; IR (neat) 2241, 1658 cm^{-1}; HRMS calcd for $C_{14}H_9ON$ 207.0684, found 207.0680.

All other products were identified by comparison of ^{1}H, ^{13}C NMR, IR, and mass spectra with those of the authentic samples or the reported values. For references, the Chemical Abstracts Service registry numbers of these products are listed below.

Diphenylmethanone (3a) [119−61−9]; **(2,4-dimethoxyphenyl)(phenyl)methanone (3b)** [3555−84−8]; **(4-chlorophenyl)(phenyl)methanone (3d)** [134−85−0]; **(2,4-dichlorophenyl)(phenyl)methanone (3e)** [19811−05−3]; **phenyl(2-thienyl)methanone (3f)** [135−00−2]; **1-phenyl-1-butanone (3 g)** [495−40−9]; **di(4-methoxyphenyl)methanone (3h)** [90−96−0]; **1-phenyl-1-hexanone (3i)** [942−92−7]; **di(4-methylphenyl)methanone (3j)** [611−97−2]; **(3-methylphenyl)(4-methylphenyl)methanone (3k)** [13152−94−8]; **(2-methylphenyl)(4-methylphenyl)methanone (3l)** [1140−16−5]; **1-(4-benzoylphenyl)ethanone (3m)** [53689−84−2]; **ethyl-4-benzoylbenzoate (3n)** [15165−27−2]; **1-naphthyl(phenyl)methanone (3o)** [642−29−5]; **9-phenanthryl(phenyl)methanone (3p)** [6453−95−8].

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