acyclic diene and must be regarded as unlikely. Studies which would allow for an unambiguous stereochemical assignment are currently in progress and will be described in the full paper on this subject.

Samuel Danishefsky,* C. F. Yan
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

P. M. McCurry, Jr.
Department of Chemistry, Carnegie-Mellon University
Pittsburgh, Pennsylvania 15213

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Selective Carbon–Carbon Bond Formation via Transition Metal Catalysis. 3.[1] A Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by the Nickel- or Palladium-Catalyzed Reaction of Aryl- and Benzylzinc Derivatives with Aryl Halides

Summary: The reaction of aryl- and benzylzinc derivatives with aryl bromides or iodides in the presence of a catalytic amount of a Ni or Pd catalyst provides a general and highly chemo- and regioselective route to unsymmetrical biaryls and diarylmethanes, the amounts of homocoupled biaryls being < 5%.

Sir: Recently, the Ni- or Pd-catalyzed reactions of organometallics containing highly electropositive main group metals, such as Li and Mg, with organic halides have provided a new approach to selective cross-coupling.[2,3] In particular, the ability of organoaluminum compounds,[1] which are generally much less reactive toward electrophiles than the corresponding Li and Mg derivatives, to readily undergo similar catalytic reactions, has been exploited in developing new cross-coupling reactions which are chemo-, regio- and stereoselective. Some of these reactions have provided synthetic procedures that are more satisfactory than those involving other organometallics, including organocuprates.[4]

We now report that organozinc compounds readily participate in the Ni- or Pd-catalyzed cross-coupling reaction, thereby providing a general and mild procedure for the preparation of unsymmetrical biaryls and diarylmethanes which features high chemo- and regioselectivity as well as high cross-/homo-coupling ratios[5,6] (eq 1).

$$\mathrm{RZnX} + \mathrm{ArX'} \xrightarrow[\text{cat. } \mathrm{Cl_2Pd(PPh_3)_2} + (i\text{-}\mathrm{Bu})_2\mathrm{AlH}]{\text{cat. } \mathrm{Ni(PPh_3)_4} \text{ or}} \mathrm{R{-}Ar} \qquad (1)$$

$$\mathrm{R} = \mathrm{Ar} \text{ or } \mathrm{ArCH_2};\ \mathrm{X} = \mathrm{Br, Cl,} \text{ or } \mathrm{Ar};\ \mathrm{X'} = \mathrm{Br} \text{ or } \mathrm{I}$$

The experimental results are summarized in Table I. The development of the procedure for the preparation of biaryls is based on the following findings. First, in order to find a class of aryl metals that are highly suited for the desired aryl–aryl cross-coupling, phenyllithium, phenylmagnesium bromide, phenylzinc chloride,[7] and phenyldiisobutylalalane[8] (50 mol % excess)[9] were treated with p-iodoanisole in the presence of 5 mol % of a catalyst prepared by the reaction of $\mathrm{Cl_2Pd(PPh_3)_2}$ with 2 equiv of diisobutylaluminum hydride (DIBAH). The results have indicated that phenyllithium is unsatisfactory, since it undergoes an extensive halogen–metal exchange reaction leading to the formation of all three expected biaryls in comparable yields. Although all the other phenylmetals gave high yields of 4-methoxybiphenyl [71% (Mg), 72% (Al), and 87% (Zn)], the amount of biphenyl formed as a by-product was considerably less with the Zn reagent (3%) than with the Mg and Al reagents (16–25%)[9] (entries 2–4), As GLC examination, after hydrolysis, of the starting arylmetals indicated the essential absence (<2%) of biphenyl, most of the biphenyl in the Mg and Al cases must have been formed in competition with the desired cross-coupling reaction.[10] These results, together with the ability of arylzinc derivatives to tolerate various electrophilic functional groups, such as nitrile and ester, make the arylzinc derivatives the reagents of choice (entries 5–8). Both arylzinc chloride and diarylzinc, which are readily

Table I. Preparation of Biaryls and Diarylmethanes by the Ni- or Pd-Catalyzed Reaction of Organometallic Reagents with Aryl Halides[a]

Entry	Organometallic reagent	ArX	Catalyst[b]	Yield[c] of Ar–Ar′ or $\mathrm{PhCH_2Ar}$, %
1	PhZnCl	p-Iodoanisole	A	85
2	PhZnCl	p-Iodoanisole	B	87
3	PhMgBr	p-Iodoanisole	B	71^{d}
4	$\mathrm{PhAl(Bu\text{-}}i)_2$	p-Iodoanisole	B	72^{e}
5	PhZnCl	p-Bromobenzonitrile	A	90
6	$\mathrm{Ph_2Zn}$	p-Bromobenzonitrile	A	85
7	PhZnCl	Methyl p-bromobenzoate	A	70
8	PhZnCl	p-Iodonitrobenzene	B	$90(74^{f})$
9	m-TolZnCl	m-Iodotoluene	A	95
10	$\mathrm{PhCH_2MgCl}$	Bromobenzene	A	80
11	$\mathrm{PhCH_2MgCl}$	Bromobenzene	B	86^{g}
12	$\mathrm{PhCH_2ZnBr}$	Methyl p-bromobenzoate	A	85^{h}
13	$\mathrm{PhCH_2MgCl}$	Methyl p-bromobenzoate	A	12^{i}
14	$\mathrm{PhCH_2ZnBr}$	p-Bromobenzonitrile	A	92
15	$\mathrm{PhCH_2MgCl}$	p-Bromobenzonitrile	A	50^{j}
16	$\mathrm{PhCH_2MgCl}$	p-Bromoanisole	A	75^{k}
17	$\mathrm{PhCH_2ZnBr}$	p-Iodonitrobenzene	B	$88(74^{f})$

[a] Unless otherwise mentioned, the temperature and time of reaction were ca. 25 °C and 1–2 h, respectively. The amount of the catalyst in each case was 5 mol %. [b] A = $\mathrm{Ni(PPh_3)_4}$ prepared in situ by the reaction of $\mathrm{Ni(acac)_2}$, $\mathrm{PPh_3}$ and $(i\text{-Bu})_2\mathrm{AlH}$ (1:4:1). B = $\mathrm{Cl_2Pd(PPH_3)_2}$ + $(i\text{-Bn})_2\mathrm{AlH}$ (1:2). [c] By GLC. Based on aryl halides introduced. The amount of biaryl in each case was <5%, and that of bibenzyl in the diarylmethane synthesis was <2%, unless otherwise mentioned. [d] The yield of biphenyl was 16%. [e] The yield of biphenyl was 25%, and the reaction was carried out at 50 °C. [f] Yield by isolation. [g] 3 h at 50 °C. [h] 6 h. [i] Although 38% of methyl p-bromobenzoate remained unreacted, benzylmagnesium chloride was consumed completely. [j] All p-bromobenzonitrile was consumed. [k] 6 h. p-Bromoanisole remained unreacted (12–13%).

obtainable by the reaction of the corresponding aryllithium with zinc chloride, are satisfactory (entries 5 and 6).

The aryl–aryl coupling reaction proceeds smoothly at room temperature even with aryl halides containing electron-donating groups, such as methoxy and methyl, which generally react less readily with Ni(0) or Pd(0) complexes than those containing electron-withdrawing groups. Both $Ni(PPh_3)_4$, preformed[11] or generated in situ by the reactions of $Ni(acac)_2$, triphenylphosphine and DIBAH, and the Pd catalyst[1b] derived from $Cl_2Pd(PPh_3)_2$ and DIBAH are satisfactory catalysts with respect to reaction rate and product yield in most cases. However, the Pd catalyst provides a unique advantage in that it is compatible with the nitro group which destroys the catalytic ability of the Ni complexes (entry 8). In no case has there been any indication of regiochemical scrambling. The procedure reported here is, of course, applicable to the preparation of symmetrical biaryls, as demonstrated by the formation of *m,m′*-bitolyl in nearly quantitative yield (entry 9).

The following procedure for the preparation of 4-nitrobiphenyl is representative. To 2.04 g (15 mmol) of zinc chloride dissolved in 25 mL of THF was added a solution of phenyllithium prepared by the reaction of 2.36 g (15 mmol) of bromobenzene and an excess of lithium in 15 mL of diethyl ether. The reaction mixture was stirred for 1 h. The Pd catalyst was prepared in a separate flask by treating 0.33 g (0.5 mmol) of dichlorobis(triphenylphosphine)palladium(II) dissolved in 15 mL of THF with 1 mL (1 mmol) of 1 *M* diisobutylaluminum hydride in hexane. To this catalyst were added 2.49 g (10 mmol) of 4-iodonitrobenzene in 30 mL of THF and the supernatant solution of phenylzinc chloride prepared above. The reaction mixture was stirred for 1 h at room temperature. After quenching with aq HCl, GLC examination of the organic layer indicated the formation of 4-nitrobiphenyl in 90% yield. Except for a trace (<2%) of biphenyl and triphenylphosphine, no other product was detected by GLC. Recrystallization (methanol) provided 1.47 g (74%) of pure 4-nitrobiphenyl: mp 112–114 °C (lit.[12] mp 114–114.5 °C); ^1H NMR (C_6D_6, TMS) δ 7.10 (d, $J = 9$ Hz, 2 H), 7.22 (s, 5 H), and 7.94 (d, $J = 9$ Hz, 2 H) ppm; IR (Nujol) 1510 (s), 1450 (s), 1330 (s), 850 (s), 770 (s), 740 (s), 700 (s), 690 (s) cm^{-1}.

The highly satisfactory results obtained with arylzinc derivatives prompted us to explore the possibility of utilizing other types of organozinc derivatives in a similar manner. In particular, benzylzinc derivatives attracted our attention. In the past, benzyl metal derivatives in general have not been extensively utilized in organic synthesis. This appears to be due mainly to the fact that the direct metalation of benzyl halides to form more reactive benzyl metals, especially those containing alkali metals such as Li,[13] is complicated by the competitive Wurtz coupling. On the other hand, benzylzinc derivatives can be obtained cleanly and often quantitatively by the direct metalation of benzyl bromides with 2–2.5 equiv of Zn powder.[14,15] Only a trace amount (<2%) of bibenzyl is formed in this reaction, whereas the corresponding Mg reaction has been accompanied by the formation of 5–10% of bibenzyl. Unfortunately, the generally low nucleophilicity of organozinc compounds has severely limited their synthetic usefulness. We reasoned that both of these characteristics could be exploited in the development of a highly chemoselective cross-coupling reaction involving benzyl groups.

We have indeed found that the above-presented procedure for the biaryl synthesis is directly applicable to the synthesis of various diarylmethanes (eq 1 and Table I).

In the absence of the Ni or Pd catalyst, essentially no diarylmethanes are formed under the otherwise comparable reaction conditions, the only detectable reaction being a very slow formation of bibenzyl presumably via slow halogen–metal exchange. Thus, the observed diarylmethane formation is catalyzed by the Ni or Pd complex. In simple cases, benzylmagnesium halides are also satisfactory reagents except for the concomitant formation of bibenzyl (entries 10 and 11). As expected, however, the benzylzinc reagent has proved to be far superior to the Mg reagent in the preparation of diarylmethanes containing electrophilic substitutents, i.e., ester and nitrile (entries 12–15).[16] The Pd-catalyzed reaction is somewhat slower than the corresponding Ni-catalyzed reaction, but the former is compatible with the nitro group which is incompatible with the latter (entry 17).

As well-documented, the reaction of aryllithiums[17] or arylmagnesium halides[18] with benzyl halides produces rapidly and in high yields bibenzyl via halogen–metal exchange. Although promising, the Cu-promoted benzyl–aryl coupling does not appear to have been well established.[19] The reaction reported here exhibits distinct advantages over the conventional Friedel–Crafts route[20,21] to diarylmethanes in that the reaction is not only completely regiospecific but is insensitive to "deactivating" functional groups, such as ester, nitrile, and nitro groups.

In summary, the aryl–aryl and aryl–benzyl coupling reaction reported here appears generally more satisfactory than any of the previously known organometallic routes, besides being highly convenient, general, and selective.

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(8) Prepared by the reaction of phenyllithium with diisobutylaluminum chloride.

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Ei-ichi Negishi,* Anthony O. King, Nobuhisa Okukado
Department of Chemistry, Syracuse University
Syracuse, New York 13210

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The Ortho Lithiation of Tertiary Benzamides

Summary: It is shown that tertiary benzamides can be metalated at the ortho position with *sec*-butyllithium–tetramethylethylenediamine at −78 °C in tetrahydrofuran; subsequent trapping of *o*-lithio-*N,N*-diethylbenzamide with deuterium oxide, methyl iodide, trimethylsilyl chloride, and benzophenone is reported.

Sir: For some time it appeared that ortho lithiations of aromatic rings would be restricted to control by substituent groups which either are not susceptible to nucleophilic addition or are deactivated toward nucleophilic attack by proton removal or initial addition.[1–4] However, within the last 2 years it has been shown that oxazolines,[5] certain piperonal cyclohexyl imines,[6] and pyrazoles[7] can retain their structural integrity and provide synthetically useful ortho lithiated intermediates. We have earlier demonstrated that the carbonyl function of a tertiary amide, an ester, or a ketone can activate the ortho hydrogen of a phenyl ring toward lithiation, but under the conditions previously used the intermediates are transient and subsequently react with starting material to give self-substituted ortho derivatives.[8–10] We now wish to report that persistent ortho lithiated species can be produced directly from tertiary benzamides and to demonstrate that these species are synthetically useful.

Reaction of *N,N*-diethylbenzamide (**1**) with *sec*-butyllithium–tetramethylethylenediamine (TMEDA) in tetrahydrofuran at −78 °C for 1 h, followed by addition of deuterium oxide, methyl iodide, trimethylsilyl chloride, or benzophenone, provides the products shown in Scheme I in the isolated yields indicated. The location of the 95 at. % of deuterium was established by ^{1}H and ^{13}C NMR spectroscopy and the location of the other substitutents was established by analytical and spectral criteria and by comparison with the properties of previously reported materials.[11] The formation of 3,3-diphenylphthalide from **2** and benzophenone provides a chemical proof of the structure of **2**. The intermediacy of **2** has extensive analogy.[1–10] The contrast between these reactions and the nucleophilic addition of *n*-butyllithium to *N,N*-dimethylbenzamide to give valerophenone[2,3,5] again points out the superiority of *sec*-butyllithium as a base.[1,12,13]

The fact that this metalation is not unduly sensitive to other substituents is demonstrated by the metalation and deuteration of **3–5** in yields of 89–95%. The case of **3** shows that under these conditions the tertiary benzamide function is more strongly activating for ortho lithiation than is the methoxy function.[2] The reaction of **4** to give a single product in which the deuterium is located between the substituents, as established by ^{13}C NMR spectroscopy,[11a] demonstrates the substituent effects can be supplementary.

These results suggest that the scope of synthetically useful ortho metalations may be wider than previously suspected. In any case, the facile formation of **2** and the ready conversions of tertiary amides to other functions offer some convenience over alternative approaches.[5,14–16] This work complements the recent report of Gschwend et al. that tertiary benzamides undergo nucleophilic addition of alkyllithiums to the amide to give species which can be ortho lithiated and allowed to

Scheme I