Synthesis of Diarylketones through Carbonylative Coupling

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1 Introduction

Carbon monoxide is the source of 'C1 chemistry' and the formation of carbon–carbon bonds involving a CO moiety is the foundation of organic chemistry. Since Roelen's discovery of the hydroformylation reaction 1938,[1] many related carbonylation reactions have been studied[2] and developed on an industrial scale.[3,4] Today carbonylation processes are used to produce, for example, n-butanal from propene (Oxo process), acetic acid from methanol (Monsanto process), and acrylic acid from acetylene or ethylene. The scope and understanding of these reactions has grown along with a desire to synthesize more complex chemicals.[5,6]

Activation of carbon monoxide necessitates the use of either 'energetic' reagents[7] or coordination to transition metals. The latter approach is the basis of homogeneous catalytic processes. Depending on the substrates used, catalytic carbonylation leads to a variety of carbonyl-containing compounds (aldehydes, ketones, carboxylic acids, esters, amides, isocyanates)[5] and dicarbonyl compounds (α-ketoacid derivatives by double carbonylation).[8]

Diarylketones are target molecules of importance for organic synthesis. An indication of their importance is provided simply by looking through the Merck Index:[9] the diarylketo moiety occurs in many natural (Cotoin, Papaveraldine) and synthetic biologically active molecules, in non-steroid anti-inflamatory drugs (Thiaprofenic acid, Ketoprofen, Piketoprofen, Suprofen, Ketorolac, Isoxepac, Amfenac, Zomepirac), in all anxiolytic benzodiazepins (as cyclic imines), and in many potent antibiotic drugs (Anthracyclin and Anthraquinone derivatives). It is also found in ultraviolet screens (Sulisobenzone, Oxybenzone, Octabenzone, Mexenone). Symmetric diarylketones and their immediate derivatives are used as ultraviolet light absorbers in paints and plastics (Benzophenone-6), and elementary sulfur detectors [Benzylimido-bis(*p*-methoxyphenyl)menthone], and are used as starting materials for dyes (Michler's ketone, Anthraquinone), acaricides (Chlorfenetol), oestrogens (Chlortrianisene), gonad-stimulating principles (Cyclofenil), and nootropic drugs (Exifone). Benzophenone itself is useful as a fixative in perfumes, and as a starting material in the manufacture of antihistamines, hypnotics, and insecticides.

The synthesis of diarylketones by Friedel–Craft-type reactions (ArH + Ar'COX) is well documented.[10] Since the preparation of the starting aryl acid halides *via* carbonylation of aryl halides has also been widely studied,[4-6] this review surveys direct, one-step synthesis of diarylketones from carbon monoxide (or a transition metal carbonyl) and two aryl moieties which do not contain a carbonyl function. At the outset, a distinction is made between those methods which allow for the formation of unsymmetrical ketones and those which do not. Three general reaction schemes can be considered:

$$\mathrm{CO + ArM + Ar'M' + [Ox] \xrightarrow{[M_t]} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar' + [Ox]MM'} \qquad \textbf{Scheme A}$$

$$\mathrm{CO + ArM + Ar'X \xrightarrow{[M_t]} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar' + MX} \qquad \textbf{Scheme B}$$

$$\mathrm{CO + ArY + Ar'X + [Red] \xrightarrow{[M_t]} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar' + [Red]XY} \qquad \textbf{Scheme C}$$

M,M' = cationic or Lewis acid species
X,Y = halogen or pseudo-halogen
$[M_t]$ = transition metal catalyst or promoter
[Ox] and [Red] are formal oxidative and reducing agents in the equilibration of the equations

Literature references for reactions of these types are gathered in Table 1. With a few exceptions, all carbonylative coupling reactions affording diarylketones involve the use of an arylmetal species, ArM, and a transition metal catalyst or reagent. In Table 1, the vertical entry refers to the nature of the transition metal catalyst or reagent $[M_t]$, if any (the first line corresponds to reactions which proceed in the absence of transition metals). The horizontal entry specifies the cationic or Lewis acid species M involved (Scheme A [plain face] or Scheme B [bold face]), if any (the first column corresponds to Scheme C [italic]).

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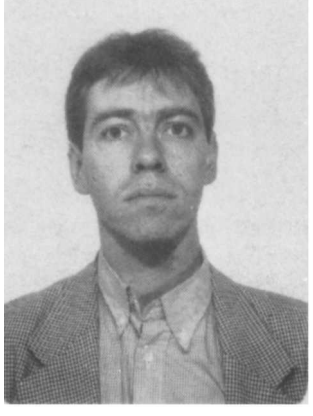


Jean-Jacques Brunet was born in Clermont-Ferrand, France, in 1945. He attended the Faculté des Sciences and the Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, where he received his chemical engineering degree in 1968. He obtained a Ph.D. (Thèse d'Etat) in Nancy in 1972 (with Professor P. Caubère). In 1985, he joined the Laboratoire de Chimie de Coordination of the CNRS (Toulouse) where he is a Research Director. Among his current research interests are organometallic chemistry and homogeneous catalysis directed towards organic synthesis, with emphasis on carbonylation reactions.

Table 1 Most significant references concerning the synthesis of diarylketones by carbonylative coupling (Scheme A: plain face; Scheme B: bold face; Scheme C: italic)

M(M') / [M$_t$]	none (Scheme C)*	Li	Mg	Hg	B	Al	Sn	Si
none		13, 14, 22						
Co	*38*			19, 20, 29				
Rh				23, 24, 25 26, 28				
Fe	*34, 36, 37 40, 41*	14						
Ni	*33*	17, 18	**32**	21, **42, 43**				
Pd	*39*			23, 24, 25 26	27, **50** **51**	**44**	**30, 31, 45 47, 48**	**49**

* X, Y = halogen or N_2X.

A detailed presentation of the most significant of these studies is undertaken in the text below. In each case, some emphasis is given to the reaction conditions, yields, scope, and limitations. We present no discussion of the proposed reaction mechanisms as they are, for the most part, hypothetical. Nevertheless, the reader may refer to references identified by an asterisk, which means that the corresponding paper includes mechanistic considerations.

2 Synthesis of Symmetrical Diarylketones

2.1 Reactions of the Type Shown in Scheme A (Ar = Ar', M = M')

2.1.1 Non-catalytic Reactions

In the early 1960's, Japanese chemists reported interesting pioneering works on the reactivity of organometallic compounds with carbon monoxide.[11,12] They found that aryllithium compounds react with carbon monoxide (−70 °C) under atmospheric pressure to yield diarylketones (equation 1),[13,14] a reaction which was later shown to give a variety of side products[15*] and to be very sensitive both to the reaction conditions and to the nature of the aryl group.[16*]

$$ArLi + CO \xrightarrow[-70\,^{\circ}C]{Et_2O} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar + \ldots. \qquad (1)$$

(Ar = C_6H_5, 2-, 3-, or 4-MeC_6H_4) 44—56%

The reaction of phenyllithium with $Fe(CO)_5$ leads to mixtures of benzaldehyde, benzhydrol and benzoin, but when the reaction is carried out using *p*-tolyllithium, 4,4'-dimethylbenzophenone is produced in 42% yield.[14] Similarly, the reaction of aryllithiums with $Ni(CO)_4$ leads mainly to acyloins, but the symmetrical diarylketone can be the major product under certain conditions ($ArLi/Ni(CO)_4 = 2.7$)(equation 2).[17*,18*] This reaction, however, does not give the expected diarylketone when *o*-tolyllithium is used.

Diarylketones are also formed in the reaction of arylmercuric bromides with equimolar amounts of dicobalt octacarbonyl under mild conditions (equation 3).[19*,20*] Although a particular

$$ArLi + Ni(CO)_4 \xrightarrow[-65\,^{\circ}C,\ 3h,\ \text{then } 60\,^{\circ}C,\ 5h]{Et_2O} \xrightarrow{H_3O^+} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar + Ar{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{OH}{|}}{CH}{-}Ar$$

(Ar = 4-Me-C_6H_4) 38% 34% (2)

work-up (addition of excess triphenylphosphine to separate $Hg[Co(CO)_4]_2$ as insoluble $Hg[Co(CO)_3PPh_3]_2$ and subsequent addition of methyl iodide to remove the excess triphenylphosphine as phosphonium iodide) is necessary for the isolation of the product, high yields are obtained.

$$ArHgBr + Co_2(CO)_8 \xrightarrow[r.t.,\ 1-2\ h]{THF} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar + Hg[Co(CO)_4]_2 + CoBr_2$$

Ar = C_6H_5, 4-FC_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4 80—93% (3)

The reaction shown in (equation 3) is not effective for perfluoro and perchloroaryl derivatives or for hindered derivatives, such as mesitylmercuric chloride, which lead only to the diarylmercurials. Intermediate behaviour was found for 2-tolymercuric bromide, which afforded the ditolylketone in 38% yield.[20*]

A similar reaction occurs with $Ni(CO)_4$ in DMF (equation 4):[21*]

$$ArHgX + Ni(CO)_4 \xrightarrow[60\ \ 70\,^{\circ}C,\ 20\ h]{DMF} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar + 2\ Hg + NiX_2 + 3\ CO$$

Ar = C_6H_5, 4-MeC_6H_4
X = Br, Cl 92—95% (4)

Although the reaction with phenylmercuric bromide can be conducted in THF as well, in the case of phenylmercuric chloride the formation of benzophenone is strongly affected by the nature of the solvent used. In DMF, DMSO, or CH_3CN, this reaction leads to benzophenone in 95—97% yield, whereas in THF or benzene it affords mainly diphenylmercury and only traces of benzophenone.

For all the above reactions, the introduced carbonyl moiety

comes from carbon monoxide itself or from a transition metal carbonyl complex It can also come from a carbamate, as shown in equation 5 for the reaction of phenyllithium (generated *in situ* from bromobenzene and excess lithium) with ethyl *N N*-diethylcarbamate [22]

$$2\,C_6H_5Li + Et_2N{-}COOEt \xrightarrow[15\ C\ 1\ h]{THF} C_6H_5{-}\underset{\underset{O}{\|}}{C}{-}C_6H_5 \quad (5)$$

82%

2 1 2 Transition Metal Catalysed Reactions

Palladium catalysts The transition metal catalysed formation of diarylketones was first reported by Henry[23] and Heck [24*] The reaction of arylmercuric chloride with carbon monoxide (3—4 bar) in acetonitrile at room temperature in the presence of catalytic amounts of Li_2PdCl_4 produces benzophenone in 29% yield, together with benzoyl chloride and biphenyl (equation 6) Diarylketones are formed preferentially to benzoyl chlorides at higher pressures of carbon monoxide [24*] To achieve a catalytic reaction, a stoichiometric amount of cupric chloride is required

$$C_6H_5HgCl + CO \xrightarrow[3—4\ bar\ r\,t\ 1\ h]{[Pd]\ CuCl_2\ CH_3CN} C_6C_5{-}\underset{\underset{O}{\|}}{C}{-}C_6H_5 \quad (6)$$

29%

$$+\ C_6H_5COCl + C_6H_5{-}C_6H_5$$

22% 2%

[Pd] (10%) = Li_2PdCl_4
$CuCl_2$ 1 equiv

A similar reaction also proceeds under very mild conditions with a much higher selectivity, using $PhPd(I)(PPh_3)_2$ in the presence of iodide ions (Bu^n_4NI) (equation 7) [25 26*]

$$2\,ArHgCl + CO \xrightarrow[1\ bar\ 20\ C\ 18\ h]{[Pd]\ Bu^n_4NI\ HMPA} Ar{-}\underset{\underset{O}{\|}}{C}{-}Ar + Hg + HgCl_2 \quad (7)$$

[Pd] (1%) = $PhPd(I)(PPh_3)_2$ 80—98%
Bu^n_4NI 1—2 equiv
Ar = C_6H_5 4 Cl C_6H_4 4 MeO C_6H_4 4 Me C_6H_4

The presence of ammonium iodide greatly increases the reaction rate It has been proposed that the role of iodide ion is to accelerate the insertion of an active Pd^0 species into the Hg—C or Hg—X bond Palladium complexes without phosphine ligands {*e g* $(MeCN)_2PdCl_2$ or $[(\eta^3\text{-}C_3H_5)PdCl]_2$} do not catalyse the above reaction

Other solvents, such as THF, DMF, and acetone, are also suitable for these catalytic reactions In acetone, sodium iodide may be used instead of ammonium iodide The reaction is also effective for the carbonylative coupling of arylmercuric acetates For instance, the use of 4-$Me_2NC_6H_4HgOAc$ affords the corresponding diaryketone in 78% yield (14 h at 20°C in DMF)

Finally, $Pd(PPh_3)_4$ has been shown to catalyse the carbonylation of arylboronic acids into a mixture of symmetrical diarylketones and methyl aroates in moderate yields (equation 8) [27]

$$ArB(OH)_2 + CO \xrightarrow[1\ bar\ 25\ C\ 20\ h]{[Pd]\ MeOH} Ar{-}\underset{\underset{O}{\|}}{C}{-}Ar + ArCOOMe \quad (8)$$

[Pd] (1—5%) = $Pd(PPh_3)_4$ 15—50% 10—25%
Ar = C_6H_5 4 Me C_6H_4 4 MeO C_6H_4

Rhodium catalysts Rhodium complexes were recognized early on as being efficient catalysts for the carbonylative coupling of arylmercuric halides (equation 9) [23 24*] Reactions using Rh catalysts generally give much less biaryl and aroyl chloride than do those using the palladium catalysts (*vide supra*, equation 6)

Under similar conditions, with $[RhCl_3,3H_2O]$ as catalyst, diphenyllead and tetraphenyltin also react to give benzophenone, though in low yield (< 10%) [23]

$$2\,ArHgCl + CO \xrightarrow[1\ \ 4\ bar\ \ 50\ \ 100\ C\ \ ?\ \ ?4\ h]{[Rh]\ toluene\ or\ CH_3CN} Ar{-}\underset{\underset{O}{\|}}{C}{-}Ar \quad (9)$$

[Rh] (1%) = $RhCl_3$ 3H O in CH_3CN or $RhCl(CO)(PR_3)_2$ in toluene 30—50%
Ar = C_6H_5 4 $MeOC_6H_4$

A more efficient catalytic system consists of a rhodium catalyst, $[Rh(CO)_2Cl]_2$ (0 5%), in the presence of LiCl (2 equiv), which considerably increases the selectivity of the reaction (equation 10) [28] The exact role of lithium chloride is not clearly understood

$$2\,ArHgCl + CO \xrightarrow[68\ \ 104\ bar\ 70\ C\ 24\ h]{[Rh]\ LiCl\ THF} Ar{-}\underset{\underset{O}{\|}}{C}{-}Ar \quad (10)$$

[Rh] (0 5%) = $[Rh(CO)_2Cl]_2$ 60—100%
LiCl 2 equiv
Ar = C_6H_5 3 NO_2 C_6H_4 2 naphthyl

This reaction (equation 10) also proceeds with heteroaromatics like 2-thiophenmercury chloride [28]

The rhodium complex $[Rh(CO)_2Cl]_2$ is also active for the carbonylative coupling of arylmercuric compounds under much milder conditions, as long as the reaction is conducted in the presence of a source of iodide ions, such as Bu^n_4NI (equation 11) [25 26*] Bis(2-thienyl)mercury also undergoes this reaction with 90% yield of the dithienylketone [26*]

$$Ar_2Hg + CO \xrightarrow[1\ bar\ 70\ C\ 18\ h]{[Rh]\ Bu_4NI\ HMPA} Ar{-}\underset{\underset{O}{\|}}{C}{-}Ar + Hg \quad (11)$$

[Rh] (0 5%) = $[Rh(CO)_2Cl]_2$ 77—89%
Bu_4NI 2 equiv
Ar = C_6H_5 4 MeC_6H_4

It is believed that in the presence of iodide ion, an anionic rhodium complex [Rh(CO)ICl] is formed, which is more active towards oxidative addition of aryl mercury compounds

THF, DMF, and acetone were also shown to be useful solvents for the reactions shown in equations 10 and 11 In acetone, NaI can be substituted for Bu^n_4NI Under these conditions, $[Rh(CO)_2Cl]_2$ is an effective catalyst precursor for the carbonylative coupling of both Ar_2Hg and ArHgX derivatives (including arylmercuric acetates) bearing functional groups such as hydroxy in the *ortho* position (95% yield of desired product), amino and dimethylamino in the *para* position (70—72% yield) [28]

Cobalt catalysts On the basis of the stoichiometric cobalt-carbonyl promoted carbonylative coupling of arylmercuric halides or diarylmercury compounds (*vide supra*),[19* 20*] a slow cobalt-catalysed carbonylation of diarylmercury compounds was devised by irradiating the reaction mixture with a Hanovia (100 W) high pressure mercury ultraviolet lamp (equation 12) [29] The reaction does not proceed with arylmercury halides Apparently, the role of the irradiation is to generate the active species, $Co_2(CO)_8$, from $Hg[Co(CO)_4]_2$, with formation of metallic mercury

$$Ar_2Hg + CO \xrightarrow[h\nu\ \ 36\ \ 233\ h]{[Co]\ THF} Ar{-}\underset{\underset{O}{\|}}{C}{-}Ar + Hg \quad (12)$$

[Co] (1 —4%) = $Co_2(CO)_8$ 52—91%
Ar = C_6H_5 4 Me C_6H_4 4 F C_6H_4
4 MeO C_6H_4 4 Cl C_6H_4

2.2 Reactions of the Type Shown in Scheme B (Ar = Ar')

All the reported syntheses of symmetrical diarylketones according to Scheme B are transition metal-catalysed Both palladium and nickel catalysts have been used

Palladium catalysts. The use of palladium catalysts for the carbonylative homocoupling of arylmercury derivatives has been shown to be effective, under more forcing conditions, for the carbonylative coupling of iodobenzene with tetraphenyltin (equation 13).[30*]

$$\underset{\text{2 equiv.}}{C_6H_5I} + (C_6H_5)_4Sn + CO \xrightarrow[\text{30 bar initial, 120 °C (overnight)}]{\text{[Pd], HMPA}} C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 + (C_6H_5)_3SnI \quad (13)$$

[Pd] (0.2%) = $(Ph_3P)_2(C_6H_5)PdI$ 68%/Ph_4Sn

A related reaction occurs between iodobenzene and phenyltrimethyltin (equation 14). For this reaction, $PhPdI(PPh_3)_2$ has been shown to be a more efficient catalyst than $[(\eta^3\text{-}C_3H_5)PdCl_2]_2$, which leads to large amounts (58%) of biphenyl.[31*]

$$C_6H_5I + C_6H_5SnMe_3 + CO \xrightarrow[\text{1 bar, 20 °C, 72 h}]{\text{[Pd], HMPA}} C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 + Me_3SnI \quad (14)$$

[Pd] (1%) = $(Ph_3P)_2(C_6H_5)PdI$ 83%

Extension of the above reaction to the synthesis of unsymmetrical diarylketones is dealt with in Section 3.2.

Nickel catalysts. Dialkylnickel complexes have been shown to catalyse the carbonylative coupling of aryl bromides with the corresponding arylmagnesium bromides under carbon monoxide at atmospheric pressure (equation 15).[32]

$$\underset{\text{190 mmol}}{C_6H_5Br} + \underset{\text{260 mmol}}{C_6H_5MgBr} + CO \xrightarrow[\text{1 bar, reflux, 24 h}]{\text{[Ni], } Et_2O} C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 \quad (15)$$

30%

$$+ (C_6H_5)_3COH + C_6H_5{-}C_6H_5$$

[Ni] (0.3%) = $Ni(C_2H_5)_2(bpy)$ 20% 16%

bpy = 2,2′-bipyridine

$NiCl_2(dppe)$ shows comparable catalytic activity for this reaction whereas $NiBr_2(PPh_3)_2$ has lower activity than the nickel complexes containing bipyridine (bpy) or dppe ligands [dppe = 1,2-bis-(diphenylphosphino) ethane].

2.3 Reactions of the Type Shown in Scheme C (Ar = Ar′)

2.3.1 Non-catalytic Reactions. Aryldiazonium salts $ArN_2^+BF_4^-$ do not react with nickel tetracarbonyl in the absence of solvent. However, addition of ethanol, t-butyl alcohol, or acetic acid to a suspension of the salt in $Ni(CO)_4$ produces evolution of carbon monoxide and nitrogen. In some cases (Ar = 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-MeO-C_6H_4) the symmetrical diarylketone is formed and may be the main reaction product (equation 16).[33*]

$$ArN_2^+BF_4^- + Ni(CO)_4 \xrightarrow{EtOH} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar + ArCO_2H + ArCO_2Et \quad (16)$$

Ar = 4-Me-C_6H_4 33% 5% 16%

Similarly, aqueous aryldiazonium chlorides react with $Fe(CO)_5$ in acetone or methanol to give the corresponding carboxylic acids, accompanied by diarylketones and aryl chlorides.[34]

Whereas $Ni(CO)_4$ reacts with various unhindered aryl iodides in THF to give the corresponding arils,[35] iron and cobalt carbonyls behave differently. For example, the reaction of iodobenzene with $Fe_3(CO)_{12}$ at 110 °C gives benzophenone (equation 17).[36,37]

$$C_6H_5I + Fe_3(CO)_{12} \xrightarrow[\text{110 °C, 50 h}]{\text{toluene}} C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 \quad (17)$$

53%

Similarly, benzophenone is formed by the reaction of iodobenzene with dicobalt octacarbonyl in THF, followed by oxidation using iodine in methanol (equation 18).[38]

$$C_6H_5I + Co_2(CO)_8 \xrightarrow[\text{70 °C, 20 h}]{THF} \xrightarrow{I_2/MeOH} C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 \quad (18)$$

45%

2.3.2 Transition Metal Catalysed Reactions

Palladium catalysts. Diaryliodonium salts react with carbon monoxide, in the presence of zinc and catalytic amounts of palladium acetate, to give mixtures of the corresponding diarylketones and diaryl α-diketones, under mild conditions (equation 19).[39]

$$[Ar{-}I{-}Ar]^+,X^- + CO + Zn \xrightarrow[\text{1 bar, r.t., 1 h}]{\text{[Pd], acetone}} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar + Ar{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}Ar + \ldots \quad (19)$$

[Pd] (5%) = $Pd(OAc)_2$ 45—60% 4—45%

Ar = C_6H_5, 4-Me-C_6H_4, 4-Bu^t-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4

X = Cl, Br

These reactions also proceed in other solvents such as DMF and nitromethane. Zinc is a more effective reducing metal than copper or tin for the conversion of Pd^{II} into Pd^0.

Iron catalysts. The reaction of iodobenzene with $[HFe(CO)_4]^-$ in a biphasic medium (benzene/aqueous NaOH) under the conditions of phase transfer (Bu_4^nNBr) allows the formation of a mixture of benzophenone, benzoic acid, and biphenyl (equation 20a).[40] Under similar conditions, a synergistic effect is observed when the reaction is carried out with a bimetallic system generated *in situ* from $Fe(CO)_5$ and $Co_2(CO)_8$ (equation 20b) (the cobalt complex alone promotes only the slow carbonylation into benzoic acid).[40] This observed synergism has not yet been explained.

This bimetallic system has been tested under non-optimized conditions for the synthesis of various diarylketones *e.g.* 4,4′-dimethylbenzophenone (57%), 4,4′-dimethoxybenzophenone (55%), 2,2′-dimethylbenzophenone (47%).[40] However, in the

C_6H_5I (H_2O/C_6H_6 = 50/30 mL)

Fe(CO)$_5$ aq. NaOH/C_6H_6; Bu_4^nNBr, CO (1 atm), 70 °C, 23 h; PhI/Fe(CO)$_5$ = 10/0.9

$$\rightarrow C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 + C_6H_5COONa + C_6H_5{-}C_6H_5 \quad (20a)$$

20% 5% 13%

Fe(CO)$_5$/$Co_2(CO)_8$ aq. NaOH/C_6H_6; Bu_4^nNBr, CO (1 atm), 70 °C, 23 h; PhI/Fe(CO)$_5$/$Co_2(CO)_8$ = 10/0.9/0.25

$$\rightarrow C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 + C_6H_5COONa + C_6H_5{-}C_6H_5 \quad (20b)$$

45% 12% 8%

case of chloro-iodobenzenes, reduction and carboxylation compete strongly with the carbonylative coupling reaction.

Recent studies involving the variation of experimental conditions for the above reaction (especially the water to benzene ratio) have pinpointed conditions where the iron reagent alone is effective for the high yield conversion of iodobenzene into benzophenone (equation 21).[41]

$$C_6H_5I \xrightarrow[NBu_4Br,\ CO\ (1\ atm),\ 70\,^{\circ}C,\ 24\ h]{Fe(CO)_5,\ aq.\ NaOH/C_6H_6} C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 + C_6H_5COONa + C_6H_5{-}C_6H_5 \quad (21)$$

PhI/$Fe(CO)_5$ = 10/3 (85% : 9% : 2%)
(H_2O/C_6H_6 = 70/10 mL)

3 Synthesis of Unsymmetrical Ketones

All the known reactions of carbonylative cross-coupling affording unsymmetrical diarylketones correspond to Scheme B. Except for one nickel-promoted reaction, they all involve catalysis by palladium complexes. These reactions are generally extensions of previously known cross-coupling reactions, carried out under carbon monoxide.

3.1 A Non-catalytic Reaction

The first transition metal mediated synthesis of an unsymmetrical diarylketone, observed in 1971[42] and improved in 1977, involved the cross-coupling of an aryl iodide with an arylmercuric halide in the presence of stoichiometric amounts of $Ni(CO)_4$ (equation 22).[43*]

$$ArI + Ar'HgX + Ni(CO)_4 \xrightarrow[60—65\,^{\circ}C,\ 10\ h]{benzene} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar' \quad (22)$$

Ar = C_6H_5, 4-Me-C_6H_4, 4-$NH_2C_6H_4$ (60—92%)
Ar' = 4-Me-C_6H_4, 4-Cl-C_6H_4, C_6H_5
X = Cl, Br

The choice of the solvent for this reaction is crucial. For example, in THF, large quantities of the symmetrical Ar'(CO)Ar' ketone are formed. In DMF, this ketone is the only reaction product, the aryl iodide remaining unchanged.

3.2 Transition Metal Catalysed Reactions

The first transition metal catalysed synthesis of unsymmetrical diarylketones, reported in 1981, involved the carbonylative cross-coupling of an aryltin derivative with an aryl iodide, catalysed by $(\eta^3\text{-}C_3H_5PdCl)_2$ under mild conditions (equation 23).[31*]

$$ArSnMe_3 + Ar'I + CO \xrightarrow[1\ bar,\ 20\,^{\circ}C,\ 1—12\ h]{[Pd],\ HMPA} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar' + Me_3SnI \quad (23)$$

[Pd] (1%) = $(\eta^3\text{-}C_3H_5PdCl)_2$ (85—99%)
Ar = C_6H_5, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-MeO-C_6H_4
Ar' = C_6H_5, 4-NO_2-C_6H_4, 4-MeOOC-C_6H_4
4-CN-C_6H_4, 4-Cl-C_6H_4

Other aprotic dipolar solvents such as DMF and acetone are useful for the above reaction, an observation which has been related to their high 'donor numbers'.

In most cases, the reaction shown in equation 23 gives nearly quantitative yields. However, in the reaction of $PhSnMe_3$ with iodobenzene, or of 2-thienyltrimethyltin with 4-iodonitrobenzene, the formation of the unsymmetrical ketone is severely hampered by the formation of the non-carbonylative coupling product. Interestingly, use of 1,4-diiodobenzene leads to the formation of 1,4-dibenzoylbenzene (78% yield).

A similar reaction, catalysed by $PdCl_2(MeCN)_2$, can be performed using arylaluminium $PhAlR_2$ (R = Ph, Bu^i) instead of aryltin derivatives (equation 24).[44] DMSO, THF, and, in some cases, THF–HMPA mixtures are the best solvents for this reaction which also proceeds with heteroaromatic iodides (Ar' = 2-thienyl).

$$C_6H_5AlR_2 + Ar'I + CO \xrightarrow[1\ bar,\ 40—50\,^{\circ}C,\ 1—4\ h]{[Pd],\ DMSO,\ or\ THF–HMPA} C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}Ar' \quad (24)$$

[Pd] (1%) = $PdCl_2(MeCN)_2$ (>90%)
Ar' = C_6H_5, 4-NO_2-C_6H_4, 4-MeO-C_6H_4
4-CN-C_6H_4, 4-Cl-C_6H_4
R = C_6H_5, Bu^t

Palladium complexes also catalyse the carbonylative cross coupling of aryltin reagents with aryltriflates (equation 25).[45]

$$ArOTf + Ar'SnBu_3 + CO \xrightarrow[1\ bar,\ 90—100\,^{\circ}C,\ 14—30\ h]{[Pd],\ LiCl,\ DMF} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar' \quad (25)$$

[Pd] (4%) = $PdCl_2$(dppf) see text (35—98%)
Ar = 3-HO-C_6H_4, 4-Br-C_6H_4,
2-MeO_2C-C_6H_4, 2-$AcOCH_2$-C_6H_4
Ar' = C_6H_5, 4-MeO-C_6H_4

Contrary to what was observed for the simple cross-coupling of aryltriflates with organotin reagents,[46] triphenylphosphine-based palladium catalysts afford the corresponding ketones in only modest to poor yields. The best results are obtained by using $PdCl_2$(dppf) (dppf = [1,1'-bis(diphenylphosphino)ferrocene]). Curiously, $PdCl_2$(dppp) gave very low yields under the same conditions. Interestingly, this carbonylative cross-coupling takes place in the presence of reactive functional groups such as aldehyde and ester on the coupling partners. However, the presence of strong electron-withdrawing groups on the organotin reagent leads to decomposition of the reactants without formation of diarylketone. As stated by the authors, the remarkable feature of this reaction is that phenols can be converted into diarylketones in two steps through replacement of the phenolic group. This group may be used in the preceeding steps to direct aromatic substitution or to effect functionalization characteristic of phenols.

Palladium(II) salts also catalyse the carbonylative coupling of arylstannanes with arenediazonium salts under low carbon monoxide pressure (equation 26).[47] The reaction takes place for X = BF_4 and PF_6, but not for X = Cl.

$$ArN_2X + (C_6H_5)_4Sn + CO \xrightarrow[9\ bar,\ r.t.,\ 6—7\ h]{[Pd],\ CH_3CN} Ar{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 \quad (26)$$

[Pd] (2%) = $Pd(OAc)_2$ (59—63%)
Ar = 4-Me-C_6H_4, 4-Br-C_6H_4
X = BF_4

The concurrent formation of benzophenone is minimized (<0.5%) by adding a mixture of ArN_2BF_4 and $Pd(OAc)_2$ to a solution of $(C_6H_5)_4Sn$ in acetonitrile after the introduction of carbon monoxide.

This palladium-catalysed process was later successfully extended to the carbonylative cross-coupling of arenediazonium salts with Ar'SnR_3 (R = Me,Et) derivatives (equation 27).[48*] The use of a mixed CH_3CN—Et_2O solvent mixture increases the reaction rate and the selectivity.

$$ArN_2BF_4 + Ar'SnR_3 + CO \xrightarrow[9\ bar,\ r.t.,\ 1—4\ h]{[Pd],\ CH_3CN–Et_2O} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar' \quad (27)$$

[Pd] (2%) = $Pd(OAc)_2$ (71—96%)

Ar = C_6H_5, 4-Me-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, 2-MeC_6H_4,
3-Me-C_6H_4, 3-Cl-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4
Ar' = C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4

This reaction is very selective no products containing an alkyl group from $Ar'SnR_3$ are observed Furthermore, neither symmetrical ketones ArC(O)Ar, nor biaryls ArAr' are formed Although the presence of an electron-withdrawing substituent on the aryl ring of the diazonium salt increases the yield of the carbonylative homocoupling product Ar'C(O)Ar', use of 4-$NO_2C_6H_4SnEt_3$ suppresses formation of the latter, giving higher yields of the dissymmetrical ketone

Palladium catalysts also effect the carbonylative cross-coupling of aryl iodides with arylfluorosilanes (equation 28) [49]

$$ArSi(R)F_2 + Ar'I + CO \xrightarrow[1\ bar\ 100°C\ 3\ 19\ h]{[Pd]\ DMI\ KF\ (1\ 1\ eq)} Ar-\overset{\overset{O}{\|}}{C}-Ar' \qquad (28)$$

R = Et, Pr^n 60—91%
[Pd] (2 5%) = $(\eta^3\text{-}C_3H_5PdCl)_2$
DMI = *N N*-dimethyl-2-imidazolinone

Ar = C_6H_5, 4-Me-C_6H_4, 3-MeO-C_6H_4
Ar' = 4-MeCOC$_6H_4$, 4-MeOOC-C_6H_4, 4-EtOC_6H_4, 3-HOCC_6H_4, 4-CN-C_6H_4, 1-naphthyl

These reactions do not proceed in THF or dioxane While the use of DMF and DMAC as solvents allows moderate yields (42—53%), *N,N*-dimethyl-2-imidazolinone (DMI) is by far the best solvent for these reactions (91% yield of ketone) The reaction is tolerant of a wide range of reactive functional groups such as ester, ketone, aldehyde, and cyano groups The presence of electron-withdrawing substituents on the aryl iodide accelerates the reaction The presence of a strong electron-withdrawing substituent, such as CF_3, on the aryl silane results in the simultaneous formation of the carboxylated product of the aryl iodide This reaction is also applicable to the synthesis of unsymmetrical heteroaryl ketones For example, the carbonylative coupling of (2-thienyl)Si(Et)F_2 with 3-iodoquinoline affords the corresponding unsymmetrical heteroarylketone (78% yield), which is barely accessible by Friedel–Crafts reaction [49]

Arylboronic acids (easily isolable and storable compounds) have been shown to be efficient reagents for the palladium-catalysed carbonylative coupling with aryl iodides (equation 29) [50]

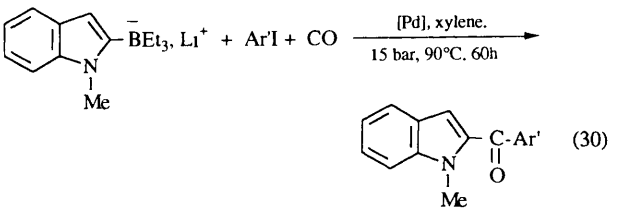
$$ArB(OH)_2 + Ar'I + CO \xrightarrow[1\ bar\ 80°C\ 5h]{[Pd]\ anisole\ K_2CO_3} Ar-\overset{\overset{O}{\|}}{C}-Ar' \qquad (29)$$

[Pd] (3%) = $(Ph_3P)_2PdCl_2$ 63—89%

Ar = C_6H_5, 4-Me-C_6H_4, 4-FC_6H_4, 4-Br-C_6H_4 2 4,6-Me_3-C_6H_2 1-naphthyl
Ar' = 4-NO_2-C_6H_4, 2-MeC_6H_4, 4-Me_2N-C_6H_4, 4-MeOOCC_6H_4, 3,4-OCH_2O-C_6H_3,

Representative palladium complexes such as $(Ph_3P)_2PdCl_2$, $(Ph_3P)_4Pd$, or $PdCl_2(PhCN)_2$ catalyse this reaction efficiently This carbonylative coupling is substantially controlled by the choice of the appropriate base and solvent The best results are obtained using K_2CO_3 and dioxane Interestingly, high yields are obtained with iodoarenes bearing electron-withdrawing groups such as 4-NO_2 (89%) or 4-COOMe (76%) Since the reaction proceeds much faster with aryl-iodide bonds than with other aryl-halogen bonds, the synthesis of diarylketones containing bromine or fluorine substituents can be carried out with high yields The carbonylative cross-coupling of 1,4-di-iodobenzene with 4-tolylboronic acid (2 equiv) affords the corresponding diketone in 82% yield Finally, this reaction is also applicable to the carbonylative coupling of phenylboronic acid with heteroaromatic iodides such as 2-iodopyridine (66%) or 3-iodothianaphthene (89%)

Recently, aryl iodides have been reported to undergo a palladium-catalyzed carbonylative cross-coupling with lithium triethyl(1-methylindol-2-yl)borate This anionic arylboron derivative is generated *in situ* from 2-lithio-1-methylindole and triethylborane [51*] The corresponding (indol-2-yl)arylketones are obtained in good yield (72—80%) (equation 30) as long as the aryl iodide does not contain an electron-withdrawing substituent (4-COOMe, 4-COMe)



(30)

[Pd] (5%) = $(Ph_3P)_2PdCl_2$ 72—80%
Ar' = C_6H_5, 2-Me-C_6H_4, 4-Me-C_6H_4, 4-Br-C_6H_4

4 Conclusion

Palladium-catalysed carbonylative cross-coupling reactions between an aryl halide (or pseudohalide) and an aryl metal of group IIB, IIIA, or IVA (Scheme B) can be carried out under mild conditions, in particular using low carbon monoxide pressures Many challenges remain, such as developing applications for the synthesis of biologically active molecules Indeed, this carbonylative aryl cross-coupling has been much less developed than that of vinyl moieties, which has been used for the synthesis of important intermediates for the synthesis of sophisticated molecules such as a capnellene derivative [52] In addition, the development of less expensive catalytic systems for these carbonylative coupling processes is always of interest Nevertheless, what remains the ultimate goal of this research area is the selective synthesis of dissymmetrical diarylketones from two aryl halides (*e g* , an aryliodide and an arylbromide) or an aryl halide and an aryl pseudohalide (triflates) (Scheme C) without using expensive and potentially hazardous arylmetal auxiliaries

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