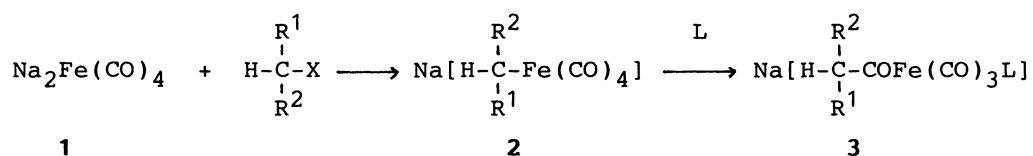


Palladium-Catalyzed Reaction of Acyliron Complexes with Aryl Halides.
A Convenient Synthesis of Aromatic Ketones

Teruyoshi KOGA, Shinako MAKINOCHI, and Nobuhisa OKUKADO*
Department of Chemistry, Faculty of Science, Kyushu University,
Hakozaki, Higashi-ku, Fukuoka 812

Acyliron complexes, easily prepared from disodium tetracarbonylferrate and alkyl halides, reacted with aryl iodides in the presence of a catalytic amount of Pd(PPh₃)₄ and a cocatalyst, ZnCl₂, to give aromatic ketones in good yields. (R)-2-Methyl-1-phenyl-1-octanone was prepared starting from (S)-2-bromooctane in an excellent optical yield.

It is well established by Collman and his coworkers that a strong nucleophile, disodium tetracarbonylferrate (1) reacts with primary or secondary alkyl halides or tosylates by typical S_N2 reaction with inversion of stereochemistry to give acyliron complexes (2), which undergo migratory insertion to afford acyliron complexes (3) with retention of stereochemistry in the presence of ligand such as CO or PPh₃.¹⁾ Thus acyliron complexes with a chiral center of the



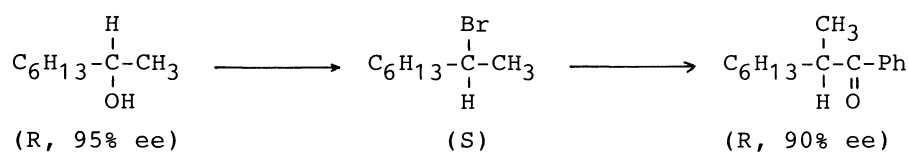
opposite configuration are obtained when the starting substrates are chiral. The acyliron complexes (3) are synthetically useful since they can be used as acyl anion equivalents. Aldehydes and carboxylic acids or their derivatives can be prepared by protolytic²⁾ or oxidative cleavage.³⁾ The acyliron complexes (3) also can be used for carbon-carbon bond formation; the reaction with reactive alkylating reagents produces unsymmetrical alkyl ketones.⁴⁾ Interestingly, (R)-3-methyl-2-nonanone was prepared in this reaction starting from (S)-1-methylheptyl tosylate in 99% optical yield.⁴⁾ However, the scope of the ketone-forming reaction is rather limited because of the low reactivity of 3; the complexes (3) seem to react with only strong alkylating agents such as primary alkyl iodides or tosylates, benzylic halides or α -chloroethers.⁴⁾ If, however, these react with the other types of organic halides, the synthetic utility of the reaction will be increased. In this paper, we wish to report a simple and efficient method for the synthesis of aromatic ketones by the Pd(PPh₃)₄ catalyzed reaction of 3 with aryl iodides in the presence of a cocatalyst, ZnCl₂.^{5,6)}

Though acyliron complexes (3) can be also prepared by various methods, e.g., such as the treatments of 1 with acyl halides⁷⁾ and of Fe(CO)₅ with organo-

lithiums,⁸⁾ those prepared from 1 and alkyl halides in the presence of PPh₃ in polar solvents was used in the present study. N-Methyl-2-pyrrolidone (NMP), which is the best solvent known for the oxidative addition of alkyl halides to 1,⁹⁾ turned out to be also most effective for the coupling reaction. Though THF-DMF mixture (1:1) is also effective, heating at 50 °C was required for the reaction to take place. The presence of the Pd-catalyst is essential. No coupling product was obtained without the catalyst. Even in the presence of the catalyst, the reaction was very slow in the absence of ZnCl₂ (<10% yield after 12 h at room temperature), however, the addition of ZnCl₂ (1-1.5 equiv.) accelerated the rate and completed the reaction within 3 h at room temperature. The reaction takes place, but proceeds only slowly with a catalytic amount of ZnCl₂ (72% yield after 12 h with 0.45 equiv. ZnCl₂).

The representative method is as follows. A mixture of Na₂Fe(CO)₄¹⁰⁾ (1, 650 μl of 0.2 M NMP solution, 0.13 mmol), octyl bromide (23 μl, 0.13 mmol), and PPh₃ (34 mg, 0.13 mmol) was stirred under nitrogen for 2 h at room temperature. To this solution of nonanoyliron complex were added phenyl iodide (10 μl, 0.1 mmol), Pd(PPh₃)₄¹¹⁾ (500 μl of 0.02 M C₆H₆ solution, 0.01 mmol), and ZnCl₂ (500 μl of 0.3 M THF solution, 0.15 mmol) and the reaction mixture was stirred at room temperature for 3 h. After usual work-up, purification by silica gel chromatography with 5% AcOEt-hexane gave 1-phenyl-1-nonanone in 81% yield.

The reactions with a variety of aryl halides carried out in the same conditions are summarized in Table 1. All the products were adequately characterized by means of the spectroscopic and elemental analyses. Primary and secondary alkyl bromides react smoothly, but tosylate does not react satisfactorily in these conditions. The toleration of various unmasked functional groups, which is one of principle advantages of Na₂Fe(CO)₄ reactions,¹⁾ holds true for these reactions as can be seen in the case of ethyl 4-bromobutanoate. The reaction with aryl iodides is smooth, but that with phenyl bromide is very sluggish. The presence of a substituent in the meta or para position on the aryl ring does not interfere the reaction, however, an ortho-substituent seems to retard the reaction, presumably, because of steric interference. Both electron attracting and releasing groups do not affect the reaction. It is noteworthy that p-iodoaniline can react without any protection. It is also worth to mention that optically active (R)-2-methyl-1-phenyl-1-octanone¹²⁾ (90% ee)¹³⁾ can be obtained from (S)-2-bromooctane, which was prepared from (R)-2-octanol (95% ee)¹⁴⁾ with (CH₃)₃SiBr according to the method reported by Jung,¹⁵⁾ though the yield of the ketone was not so good in this case (41%).¹⁶⁾ This means that the conversion of the bromide to the ketone occurred at least in 95% optical yield.¹⁷⁾



The reaction can be considered to proceed through reductive elimination of an acyl-organopalladium(II) complex which is formed by the transmetalation of an acyliron complex with an organopalladium(II) halide complex, generated by

Table 1. Reaction of acyliron complexes with aryl halides^{a)}

Entry	RX	$\frac{\text{Na}_2\text{Fe}(\text{CO})_4}{\text{PPh}_3, \text{NMP}}$	$\text{Na}[\text{RCOFe}(\text{CO})_3\text{L}]$	$\frac{\text{ArX}', \text{ZnCl}_2}{\text{Pd}(\text{PPh}_3)_4}$	RCOAr
	RX	ArX'	Conditions ^{b)}	Yield ^{c)} /%	
1	n-OctBr	PhI	rt (3 h)	81 (90)	
2	n-BuBr	PhI	rt (3 h)	71 (80)	
3	i-BuBr	PhI	rt (3 h)	72 (92)	
4	i-BuBr	PhBr	50 °C (3 h)	(17)	
5	i-PrBr	PhI	rt (3 h)	56 (82)	
6	s-BuOTs	PhI	rt (3 h)	(27) ^{d)}	
7	$\text{EtOOC}(\text{CH}_2)_3\text{Br}$	PhI	rt (3 h)	76	
8	i-BuBr	o-CH ₃ -PhI	50 °C (3 h)	(30)	
9	i-BuBr	m-CH ₃ -PhI	rt (3 h)	86	
10	i-BuBr	p-CH ₃ -PhI	rt (3 h)	74	
11	i-BuBr	p-CH ₃ O-PhI	rt (3 h)	72 (79)	
12	i-BuBr	p-NH ₂ -PhI	rt (3 h)	58	
13	i-BuBr	p-CH ₃ OC-PhI	rt (3 h)	57	
14	i-BuBr	p-CH ₃ OOC-PhI	rt (3 h)	69	

a) All reactions were carried out as described in the text unless otherwise mentioned. b) The conditions for the coupling reactions. c) Isolated yield. Number in parenthesis is GLC yield. d) A mixture of THF-NMP(3:1) was used as the solvent. No product was obtained in NMP.

oxidative addition of aryl halide to the Pd(0) catalyst.¹⁸⁾ Such acyl-organo-palladium(II) intermediates were also assumed in a number of ketone synthesis reactions, such as Pd-mediated reactions of acyl chlorides with organotins,¹⁹⁾ organozincs,²⁰⁾ and organomercurials.²¹⁾ The cocatalyst, ZnCl₂, seems to facilitate the transmetallation step as reported before.⁶⁾ Unfortunately, however, the exact role of ZnCl₂ is not clear and has been left to be clarified.

Studies on reactions of acyliron complexes with other types of organic halides in the presence of Pd catalysts are under progress.

References

- 1) J.P.Collman, *Acc.Chem.Res.*, **8**,342(1975) and references cited therein.
- 2) M.P.Cooke, *J.Am.Chem.Soc.*, **92**,6080(1970).
- 3) J.P.Collman, S.R.Winter, and R.G.Komoto, *J.Am.Chem.Soc.*, **95**,249(1973).
- 4) J.P.Collman, S.R.Winter, and D.R.Clark, *J.Am.Chem.Soc.*, **94**,1788(1972).
- 5) For Pd-catalyzed reactions, see R.F.Heck, "Palladium Reagents in Organic Syntheses," Academic Press, London (1985); B.M.Trost and T.R.Verhoven, "Comprehensive Organometallic Chemistry," ed by G.Willkinson, Pergamon Press, Oxford(1982), Vol.8, p.799; E.Negishi, *Acc.Chem.Res.*, **15**,340(1982).
- 6) For ZnCl₂ as a cocatalyst in Pd-catalyzed reactions, see E.Negishi, N.Okukado, A.O.King, D.E.Van Horn, and B.I.Spiegel, *J.Am.Chem.Soc.*, **100**,2254(1978).

- 7) Y.Watanabe, T.Mitsudo, M.Tanaka, K.Yamamoto, T.Okajima, and Y.Takegami, *Bull.Chem.Soc.Jpn.*, 44,2569(1971).
- 8) Y.Sawa, M.Ryang, and S.Tsutsumi, *Tetrahedron Lett.*, 1969,5189.
- 9) J.P.Collman, R.G.Finke, J.N.Cawse, and J.I.Brauman, *J.Am.Chem.Soc.*, 99,2515 (1977).
- 10) $\text{Na}_2\text{Fe}(\text{CO})_4 \cdot 1.5$ dioxane was prepared by reduction of $\text{Fe}(\text{CO})_5$ with sodium benzophenone ketyl in boiling dioxane and stored in NMP;1)
- 11) D.R.Coulson, *Inorg.Synth.*, 13,121(1972).
- 12) Optically active (R)-2-methyl-1-phenyl-1-octanone has been prepared by alkylation of 2-lithio-2-phenyl-1,3-dithiane with (S)-2-iodooctane, followed by hydrolysis. $[\alpha]_D -21.5^\circ$ (c 5, ether); D.Seebach, D.Steinmuller, and F.Demuth, *Angew.Chem.Int.Ed.Engl.*, 7,620(1962); by Friedel-Crafts reaction with (R)-2-methyloctanoyl chloride, $[\alpha]_{5805}^{20} -29.7^\circ$ (c 1.8, C_6H_6); K.Maruyama, H.Iwamoto, O.Soga, and A.Takuwa; *Bull.Chem.Soc.Jpn.*, 55,2161 (1972). However, optical purities of these products were not reported.
- 13) The absolute configuration was determined by the optical rotation of the product, $[\alpha]_D^{20} -19.9^\circ$ (c 4.9, ether). The optical purity was determined as follows. After some unsuccessful attempts with NMR using various chiral shift reagents, the product was reduced with NaBH_4 at low temperature. A pair of the major diastereomer, mainly consisting of (1R,2R)-isomer predicted from Cram's rule, was separated cleanly with preparative TLC and converted to (S)-MTPA esters, the diastereomeric ratio of which was determined with ^1H NMR (400 MHz).
- 14) The optical purity was also determined after conversion to (S)-MTPA ester.
- 15) M.E.Jung and G.L.Hatfield, *Tetrahedron Lett.*, 1978,4483. The bromide obtained had $[\alpha]_D^{20} +38.4^\circ$ (neat), 87% ee based on $[\alpha]_D^{20} +44.1^\circ$ (neat); H.R.Hudson, *Synthesis*, 1969,112.
- 16) Optimization of the conditions was not carried out.
- 17) We could not determine the optical purity of the bromide with the same accuracy with those of the alcohol and the ketone. However, considering the claim by Jung that the bromination reaction proceeds in 93.8% inversion and the ee value(87%) estimated from the optical rotation, the conversion of the bromide to the ketone can be regarded to proceed with almost complete inversion of stereochemistry.
- 18) K.Tamao, K.Sumitani, and M.Kumada, *J.Am.Chem.Soc.*, 94,4374(1972).
- 19) D.Milstein and J.K.Stille, *J.Am.Chem.Soc.*, 100,3636(1978) and references cited therein; M.W.Logue and K.Teng, *J.Org.Chem.*, 47,2549(1982).
- 20) T.Sato, K.Naruse, M.Enokiya, and T.Fujisawa, *Chem.Lett.*, 1981,1135; T.Sato, T.Ito, and T.Fujisawa, *ibid.*, 1982,1559; E.Negishi, V.Bagheri, S.Chatterjee, F.-T.Luo, J.A.Miller, and A.T.Stoll, *Tetrahedron Lett.*, 24, 5181(1983); Y.Tamaru, H.Ochiai, F.Sanda, and Z.Yoshida, *ibid.*, 26,5529(1985); Y.Tamaru, H.Ochiai, T.Nakamura, K.Tsubaki, and Z.Yoshida, *ibid.*, 26,5559(1985).
- 21) K.Takagi, T.Okamoto, Y.Sakagibara, A.Ohno, S.Oka, and N.Hayama, *Chem. Lett.*, 1975,951; R.C.Larock and J.C.Bernhardt, *J.Org.Chem.*, 43,710(1978).

(Received April 1, 1988)