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Bis(cyclopentadienyldicarbonyliron) as a Convenient Carbon Monoxide Source in Palladium-catalyzed Carbonylative Coupling of Aryl Iodides with Amines, Alcohols, and Thiols

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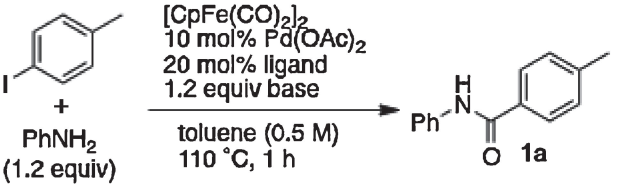
Bis(cyclopentadienyldicarbonyliron) ($[CpFe(CO)_2]_2$) serves as a carbon monoxide source in carbonylative coupling reactions. Treatment of aryl iodides with primary amines in the presence of DBU and $[CpFe(CO)_2]_2$ under palladium catalysis provides the corresponding benzamides in good yields. Similar reactions with phenols and thiols provide the corresponding benzoate esters and thioesters, respectively. A catalytic amount of DMAP as an additive promoted the carbonylative coupling reactions with primary alcohol and secondary amine.

Transition-metal-catalyzed carbonylative cross-coupling reactions in the presence of carbon monoxide are useful methods for synthesizing carbonyl compounds.[1–3] Because of the inherent difficulty in handling highly toxic carbon monoxide, considerable efforts have been made to develop carbon monoxide equivalents to achieve CO-gas-free carbonylation.[4] Organic carbonyl compounds such as pentafluorobenzaldehyde and *N*,*N*-dimethylformamide are known to serve as carbon monoxide equivalents.[5–7] However, the scope of substrates and hence the diversity of products are limited. Alternatively, metal carbonyl complexes are also useful as carbon monoxide sources since they emit carbon monoxide upon heating. $[Ni(CO)_4]$ was first used stoichiometrically in carbonylative reactions.[8] Because of the high toxicity of the nickel complex, palladium-catalyzed reactions with safer solid metal carbonyls such as $[Mo(CO)_6]$,[9] $[Cr(CO)_6]$,[9b] and $[W(CO)_6]$[9b,9h,9i] have been developed.[10]

Iron is a ubiquitous, inexpensive, and nontoxic transition metal, and iron compounds have thus been attracting increasing attention in organic synthesis.[11] Despite the superiority of iron over molybdenum, chromium, and tungsten, $[Fe(CO)_5]$ and $[Fe_3(CO)_{12}]$ were reported to be unreactive for palladium-catalyzed carbonylative coupling.[9b] This was indeed the case, and our attempts to use the simple iron carbonyl complexes resulted in failure. Instead, we found that economical and easy-to-handle bis(cyclopentadienyldicarbonyliron) ($[CpFe(CO)_2]_2$) serves as a source of carbon monoxide in palladium-catalyzed carbonylative coupling for synthesizing aromatic amide (Table 1). Treatment of 4-iodotoluene with aniline in the presence of a catalytic amount of palladium acetate, $[CpFe(CO)_2]_2$ (1.5 equiv), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene for 1 h provided expected amide **1a** quantitatively (Entry 1). It is worth noting that other iron carbonyl complexes such as $[CpFe(CO)_2I]$, $[Cp^*Fe(CO)_2]_2$, $[Cp^*Fe(CO)_2I]$, and $[Fe_2(CO)_9]$ were useless under the reaction conditions and that almost no conversions were observed.[12]

Table 1. Optimization of conditions



Entry	$[CpFe(CO)_2]_2$/equiv	Ligand	Base	Yield[a]/%
1	1.5	none	DBU	100
2	0.75	none	DBU	96
3	0.38	none	DBU	70
4	0.38	PPh_3	DBU	69
5	0.38	$P(c\text{-}C_6H_{11})_3$	DBU	79
6	0.38	DPPE	DBU	43
7	0.38	$P(c\text{-}C_6H_{11})_3$	DBN	69

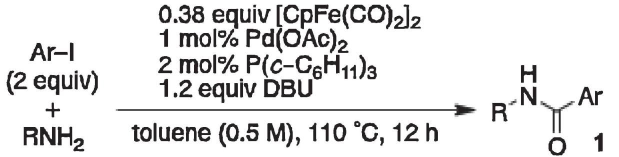
[a]The remainder of mass balance was unreacted 4-iodotoluene.

Since 1.5 equiv of $[CpFe(CO)_2]_2$ corresponds to 6 equiv of carbon monoxide, we thus tried to reduce the amount of $[CpFe(CO)_2]_2$. The amount of $[CpFe(CO)_2]_2$ could be reduced to 0.75 equiv without significantly deteriorating the yield (Entry 2). In the presence of 0.38 equiv of $[CpFe(CO)_2]_2$ (1.5 equiv of CO), the reaction proceeded cleanly to afford a 70% yield of **1a**, the remainder of mass balance being unreacted 4-iodotoluene (Entry 3). To increase the efficiency of the reaction with 0.38 equiv of $[CpFe(CO)_2]_2$, we further examined the effect of ligand. Tricyclohexylphosphane slightly improved the yield to 79% (Entry 5) whereas triphenylphosphane and bidentate 1,2-bis(diphenylphosphano)ethane had no and adverse effects, respectively (Entries 4 and 6). The choice of strong organic bases such as DBU and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, Entry 7) is critical. Other organic bases such as 1,4-diazabicyclo[2.2.2]octane, tributylamine, and pyridine as well as inorganic bases such as cesium carbonate and potassium *t*-butoxide failed to promote the reaction. In analogy with the molybdenum-mediated carbonylation,[9b] DBU would strongly coordinate to iron, which leads to irreversible release of carbon monoxide from iron carbonyl complexes.

Finally, the use of 2 equiv of iodobenzene and a prolonged reaction time could improve the yield of **1b** (based on 4-toluidine) while reducing the amount of the palladium catalyst to 1 mol % (Table 2, Entry 1).[13] A variety of benzamides were synthesized under the optimized reaction conditions. Primary amines, both aromatic and aliphatic, reacted smoothly to afford the corresponding benzamides in good yields (Entries 1–7). The electronic as well as steric nature of anilines did not influence the efficiency of the reaction. The scope of aryl iodides is wide (Entries 8–10) although the yield of **1l** was moderate because a part of the acetyl groups reacted with aniline to yield the corresponding imine (Entry 11). Bulky 9-iodoanthracene was less reactive (Entry 12). Aside from aryl iodide, β-iodostyrene reacted to afford cinnamamide **1n** (Entry 13).

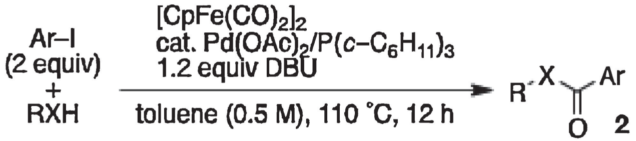
Phenols and alkanethiol are good partners in the carbonylative coupling reactions (Table 3). In the reactions with alkanethiol, larger amounts of the iron complex and the palladium catalyst were essential to achieve satisfactory results (Entries 7–11). The reaction with aromatic benzenethiol afforded **2l** in moderate yield (Entry 12). Compared to carbonylative amidation and esterification, synthesis of thioesters by carbonylation of aryl halides under an atmosphere of carbon monoxide is difficult.[14] Our approach to thioesters is much more efficient, user-friendly, and thus useful.

Table 2. Synthesis of benzamides



Entry	Ar	R	1	Yield/%
1	Ph	4-MeC_6H_4	**1b**	96
2	Ph	4-$MeOC_6H_4$	**1c**	80
3	Ph	4-$CF_3C_6H_4$	**1d**	74
4	Ph	4-NCC_6H_4	**1e**	87
5	Ph	2-FC_6H_4	**1f**	96
6	Ph	1-naphthyl	**1g**	70
7	Ph	n-$C_{12}H_{25}$	**1h**	76
8	4-$MeOC_6H_4$	Ph	**1i**	73
9	4-$EtO_2CC_6H_4$	Ph	**1j**	78
10	2-MeC_6H_4	Ph	**1k**	79
11	4-AcC_6H_4	Ph	**1l**	46
12	9-anthracenyl	Ph	**1m**	36
13	[(E)-PhCH=CH]	Ph	**1n**	51

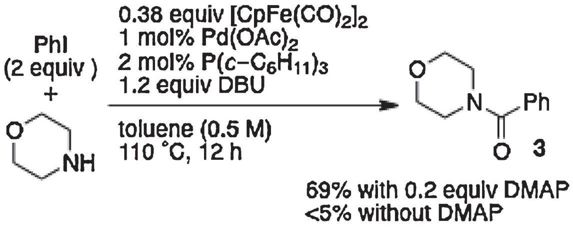
Table 3. Synthesis of benzoates and benzothioates[a]



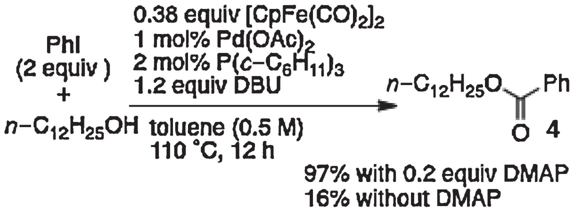
Entry	Ar	RXH	2	Yield/%
1	Ph	4-BuC_6H_4OH	**2a**	81
2	Ph	4-$MeOC_6H_4OH$	**2b**	78
3	Ph	4-$CF_3C_6H_4OH$	**2c**	63
4	Ph	1-naphthol	**2d**	72
5	4-$MeOC_6H_4$	PhOH	**2e**	63
6	4-$EtO_2CC_6H_4$	PhOH	**2f**	70
7	Ph	n-$C_{12}H_{25}SH$	**2g**	77
8	4-$MeOC_6H_4$	n-$C_{12}H_{25}SH$	**2h**	88
9	4-$EtO_2CC_6H_4$	n-$C_{12}H_{25}SH$	**2i**	70
10	4-FC_6H_4	n-$C_{12}H_{25}SH$	**2j**	73
11	1-naphthyl	n-$C_{12}H_{25}SH$	**2k**	60
12	Ph	PhSH	**2l**	45

[a]Conditions for esterification: 0.38 equiv $[CpFe(CO)_2]_2$, 1 mol % $Pd(OAc)_2$, 2 mol % tricyclohexylphosphane. Conditions for thioesterification: 1.5 equiv $[CpFe(CO)_2]_2$, 10 mol % $Pd(OAc)_2$, 20 mol % tricyclohexylphosphane.

The reaction with a secondary amine, morpholine, was sluggish under the standard reaction conditions (eq 1). Gratifyingly, a catalytic amount of 4-dimethylaminopyridine (DMAP) as an additive improved the yield of **3**.[15] The effect of DMAP was applicable to the reaction with primary alcohol (eq 2).



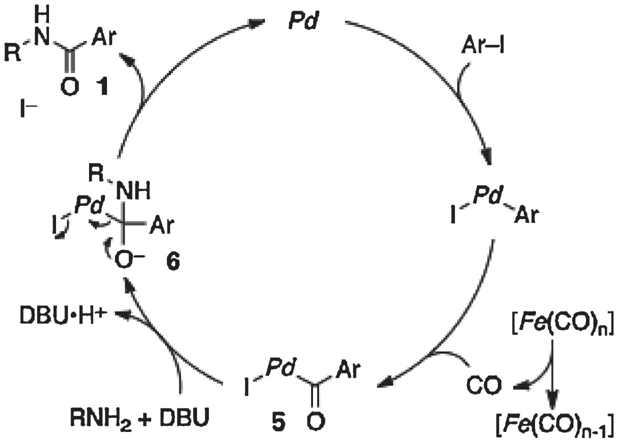
(1)



(2)

Considering the effect of DMAP, we assume the reaction mechanism as shown in Scheme 1. Oxidative addition would be followed by insertion of CO that is generated by thermolysis of iron carbonyl complexes.[16] The resulting acylpalladium iodide **5** would undergo DBU-mediated nucleophilic attack at the carbonyl moiety with a nucleophile.[17] Departure of an iodide and the initial zerovalent palladium from **6** should yield the product. DMAP would attack acylpalladium **5** at the carbonyl moiety to generate the corresponding highly reactive acylpyridinium intermediate, which allows hindered secondary amine and less nucleophilic aliphatic alcohol to participate in the nucleophilic substitution.

In conclusion, we have found that $[CpFe(CO)_2]_2$ is an efficient carbon monoxide source in palladium-catalyzed amidation, esterification, and thioesterification of aryl iodides with amines, alcohols, and thiols. Notably, the synthesis of thioesters



Scheme 1. Plausible reaction mechanism.

with $[CpFe(CO)_2]_2$ is a much safer and efficient protocol than the previously reported reactions employing carbon monoxide gas of high pressure.[18]

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References and Notes

1 Reviews: a) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. b) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E. Negishi, A. de Meijere, Wiley, New York, **2002**, Vol. 2, Chap. 6. c) J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**.

2 Pioneering work: a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318. b) A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327.

3 Very recent selected examples: a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2010**, *5*, 2168. b) B. Roberts, D. Liptrot, L. Alcaraz, *Org. Lett.* **2010**, *12*, 1264. c) G. Chouhan, H. Alper, *Org. Lett.* **2008**, *10*, 4987. d) C. Csajági, B. Borcsek, K. Niesz, I. Kovács, Z. Székelyhidi, Z. Bajkó, L. Ürge, F. Darvas, *Org. Lett.* **2008**, *10*, 1589. e) J. Salvadori, E. Balducci, S. Zaza, E. Petricci, M. Taddei, *J. Org. Chem.* **2010**, *75*, 1841. f) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7102. g) D. A. Watson, X. Fan, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7096. h) S. A. Worlikar, R. C. Larock, *J. Org. Chem.* **2008**, *73*, 7175. i) A. Fusano, T. Fukuyama, S. Nishitani, T. Inouye, I. Ryu, *Org. Lett.* **2010**, *12*, 2410. j) K. Kobayashi, Y. Nishimura, F. Gao, K. Gotoh, Y. Nishihara, K. Takagi, *J. Org. Chem.* **2011**, *76*, 1949.

4 T. Morimoto, K. Kakiuchi, *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.

5 Rh-Catalyzed intramolecular lactamization by using aldehydes as CO sources: a) T. Morimoto, M. Fujioka, K. Fuji, K. Tsutsumi, K. Kakiuchi, *Chem. Lett.* **2003**, *32*, 154. b) T. Morimoto, M. Fujioka, K. Fuji, K. Tsutsumi, K. Kakiuchi, *J. Organomet. Chem.* **2007**, *692*, 625.

6 Pd-Catalyzed carbonylative reactions with DMF as a CO source providing *N*,*N*-dimethyl- or *N*-benzylbenzamides: Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6232.

7 Pd-Catalyzed reactions with formates or DMF as acyl anion equivalents: a) J.-F. Carpentier, Y. Castanet, J. Brocard, A. Mortreux, F. Petit, *Tetrahedron Lett.* **1991**, *32*, 4705. b) P. J. Tambade, Y. P. Patil, M. J. Bhanushali, B. M. Bhanage, *Tetrahedron Lett.* **2008**, *49*, 2221. c) Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Comb. Chem.* **2003**, *5*, 82. d) J. Ju, M. Jeong, J. Moon, H. M. Jung, S. Lee, *Org. Lett.* **2007**, *9*, 4615. e) K. Hosoi, K. Nozaki, T. Hiyama, *Org. Lett.* **2002**, *4*, 2849. f) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* **2003**, *5*, 4269. g) P. Berger, A. Bessmernykh, J.-C. Caille, S. Mignonac, *Synthesis* **2006**, 3106. h) S. Ko, C. Lee, M.-G. Choi, Y. Na, S. Chang, *J. Org. Chem.* **2003**, *68*, 1607. i) R. F. Cunico, R. K. Pandey, *J. Org. Chem.* **2005**, *70*, 9048.

8 a) N. L. Bauld, *Tetrahedron Lett.* **1963**, *4*, 1841. b) M. Nakayama, T. Mizoroki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 508. c) E. J. Corey, L. S. Hegedus, *J. Am. Chem. Soc.* **1969**, *91*, 1233.

9 a) N.-F. K. Kaiser, A. Hallberg, M. Larhed, *J. Comb. Chem.* **2002**, *4*, 109. b) J. Wannberg, M. Larhed, *J. Org. Chem.* **2003**, *68*, 5750. c) O. Lagerlund, M. Larhed, *J. Comb. Chem.* **2006**, *8*, 4. d) X. Wu, J. Wannberg, M. Larhed, *Tetrahedron* **2006**, *62*, 4665. e) L. R. Odell, J. Sävmarker, M. Larhed, *Tetrahedron Lett.* **2008**, *49*, 6115. f) O. Lagerlund, M. L. H. Mantel, M. Larhed, *Tetrahedron* **2009**, *65*, 7646. g) J. Lindh, A. Fardost, M. Almeida, P. Nilsson, *Tetrahedron Lett.* **2010**, *51*, 2470. h) B. Roberts, D. Liptrot, L. Alcaraz, T. Luker, M. J. Stocks, *Org. Lett.* **2010**, *12*, 4280. i) A. Więckowska, R. Fransson, L. R. Odell, M. Larhed, *J. Org. Chem.* **2011**, *76*, 978. j) M. Iizuka, Y. Kondo, *Eur. J. Org. Chem.* **2007**, 5180.

10 Molybdenum and tungsten carbonyl primary amine complexes in carbamoylation: a) W. Ren, M. Yamane, *J. Org. Chem.* **2009**, *74*, 8332. b) W. Ren, M. Yamane, *J. Org. Chem.* **2010**, *75*, 3017.

11 Reviews: a) A. J. Pearson, *Iron Compounds in Organic Synthesis*, Academic Press, London, **1994**. b) H.-J. Knölker, *Curr. Org. Synth.* **2004**, *1*, 309. c) H.-J. Knölker, *Chem. Rev.* **2000**, *100*, 2941. d) K. Rück-Braun, M. Mikulás, P. Amrhein, *Synthesis* **1999**, 727. e) S. Kawamura, K. Ishizuka, H. Takaya, M. Nakamura, *Chem. Commun.* **2010**, *46*, 6054, and references cited therein. f) A. Rudolph, M. Lautens, *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. g) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500. h) W. M. Czaplik, M. Mayer, J. Cvengroš, A. J. von Wangelin, *ChemSusChem* **2009**, *2*, 396. i) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, *75*, 6061.

12 The reason for the unique reactivity of $[CpFe(CO)_2]_2$ is not clear. $[CpFe(CO)_2I]$ and $[Cp^*Fe(CO)_2I]$ reacted with aniline under the reaction conditions to yield amido irons. $[Cp^*Fe(CO)_2]_2$ has a bulky Cp^* group and is more electron-rich and DBU might coordinate less tightly to the iron center. For the effect of DBU, see ref. 9b.

13 Experimental procedure: Palladium acetate (1.1 mg, 0.0050 mmol) was placed in a 5-mL glass pressure vial under argon. Tricyclohexylphosphane (1.0 M toluene solution, 0.010 mL, 0.010 mmol) and toluene (1.0 mL) were then added. After the mixture was stirred for 10 min, 4-toluidine (54 mg, 0.50 mmol), iodobenzene (0.11 mL, 1.0 mmol), $[CpFe(CO)_2]_2$ (66 mg, 0.19 mmol), and DBU (90 µL, 0.60 mmol) were sequentially added at room temperature. The vial was sealed with a poly(tetrafluoroethylene)–silicone septum and heated at 110 °C for 12 h. The product was passed through a pad of Florisil by using dichloromethane as an eluent. The filtrate was concentrated in vacuo. Chromatographic purification on silica gel (dichloromethane) provided **1b** (101 mg, 0.48 mmol) in 96% yield.

14 The precedented reactions required 10–30 atm of carbon monoxide: a) H. Cao, L. McNamee, H. Alper, *J. Org. Chem.* **2008**, *73*, 3530. b) Y. Hu, J. Liu, Z. Lü, X. Luo, H. Zhang, Y. Lan, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 3153.

15 A similar effect of DMAP was reported in palladium-catalyzed carbonylation reactions. See ref. 9e.

16 When the reaction was performed in an unsealed reaction flask under argon, no reaction took place because of the loss of CO from the reaction mixture. Thermolysis should hence provide free CO. Direct transfer of CO from iron to palladium is unlikely.

17 As a minor process, ligand exchange between iodide and amine yielding the corresponding acylpalladium amide and the following reductive elimination can afford the product.

18 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.