Synthetic Methods

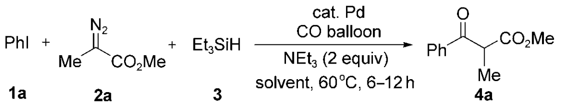
DOI: 10.1002/anie.200906349

Palladium-S57alyzed Carbonylation/Acyl Migratory Insertion Sequence**

*u , Lu , M xC G , u , , J **

Migratory insertion is one of the fundamen7al processes in organopalladium chemistry. In particular, migratory insertion of a CO ligand and the formation of reactive acylpalladium intermediate is a powerful method for introducing a carbonyl functionality into organic molecules. The ca7alytic cycle involving such a key step has been developed into one of the most important tools to synthesize various carbonyl compounds.[1] However, for a long time, the scope of migratory insertion processes of organopalladium has been limited to those involving carbon monoxide. In view of the similarity between a carbene and carbon monoxide, one may conceive palladium–carbene as another species which may undergo migratory insertion (Scheme 1). Indeed, the migratory insertion process has been reported for stable palladium–carbene species.[2] More recently, catalytic reactions which are proposed to includeTD[(h2r39.ory9w751.7tatory)-354.836.3(scoed)-335aoed pa79.5(m1.2787Td)-3[(ttermediat7Td).7(rhaveTD[(pro6(has)d

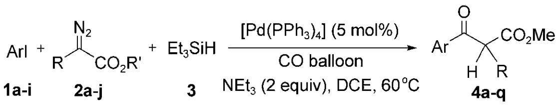
Table 1: Conditions for the palladium-catalyzed reaction of CO with 1a and 2a.[a]



Entry	Cat. (mol%)	Solvent	Yield [%][b]
1	[Pd(PPh$_3$)$_4$] (5)	DCE	88
2	[Pd(PPh$_3$)$_4$] (5)	toluene	50
3	[Pd(PPh$_3$)$_4$] (5)	dioxane	73
4	[Pd(PPh$_3$)$_4$] (5)	MeCN	75
5	Pd(PPh$_3$)$_4$(5)	DMF	21
6	[Pd(PPh$_3$)$_4$] (5)	CHCl$_3$	84
7	Pd(OAc)$_2$ (5)	DCE	< 5
8	[Pd(PPh$_3$)$_2$Cl$_2$] (5)	DCE	70
9	[Pd$_2$(dba)$_3$] (2.5)	DCE	40
10	[Pd$_2$(dba)$_3$] (2.5)/PPh$_3$ (5)	DCE	46
11	[Pd$_2$(dba)$_3$] (2.5)/PPh$_3$ (10)	DCE	65
12	[Pd$_2$(dba)$_3$] (2.5)/dppb (5)	DCE	54
13	[Pd$_2$(dba)$_3$] (2.5)/[HP*n*Bu$_3$]BF$_4$ (10)	DCE	31
14	[Pd$_2$(dba)$_3$] (2.5)/P*t*Bu$_3$ (10)	DCE	25
15	[Pd$_2$(dba)$_3$] (2.5)/[HPCy$_3$]BF$_4$ (10)	DCE	33
16	none	DCE	0

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), and **3** (1.1 equiv). [b] Yield of isolated product. dba = dibenzylideneacetone, DMF = *N,N*-dimethylformamide, Cy = cyclohexyl.

Table 2: [Pd(PPh$_3$)$_4$]-catalyzed reactions of CO with **1a–i** and **2a–j**.[a]



Entry	1: Ar	2: R, R'	*t* [h]	Yield of 4, [%][b]
1	**1a**: C$_6$H$_5$	**2a**: Me, Me	10	**4a**: 88
2	**1b**: *o*-MeC$_6$H$_4$	**2a**: Me, Me	11	**4b**: 43[c]
3	**1c**: *p*-MeC$_6$H$_4$	**2a**: Me, Me	9	**4c**: 80
4	**1d**: *p*-MeOC$_6$H$_4$	**2a**: Me, Me	9	**4d**: 85
5	**1e**: *p*-NO$_2$C$_6$H$_4$	**2a**: Me, Me	17	**4e**: 61
6	**1f**: *p*-MeO$_2$CC$_6$H$_4$	**2a**: Me, Me	14	**4f**: 74
7	**1g**: *p*-ClC$_6$H$_4$	**2a**: Me, Me	10	**4g**: 80
8	**1a**: C$_6$H$_5$	**2b**: Me, *i*Pr	7	**4h**: 87
9	**1a**: C$_6$H$_5$	**2c**: Ph(CH$_2$)$_3$, Me	12	**4i**: 77
10	**1a**: C$_6$H$_5$	**2d**: Ph, Me	9	**4j**: 57
11	**1a**: C$_6$H$_5$	**2e**: *p*-MeOC$_6$H$_4$, Me	8	**4k**: 75
12	**1h**: *m*-CH$_3$C$_6$H$_4$	**2a**: Me, Me	10	**4l**: 64
13	**1i**: *p*-BrC$_6$H$_4$	**2a**: Me, Me	10	**4m**: 75
14	**1a**: C$_6$H$_5$	**2f**: Me, *t*Bu	12	**4n**: 82
15	**1a**: C$_6$H$_5$	**2g**: Me, Bn	12	**4o**: 79
16	**1a**: C$_6$H$_5$	**2h**: *n*Pr, Me	10	**4p**: 66
18	**1a**: C$_6$H$_5$	**2i**: Bn, Me	20	**4q**: 62
19	**1a**: C$_6$H$_5$	**2j**: *p*-O$_2$NC$_6$H$_4$, Me	12	–[d]

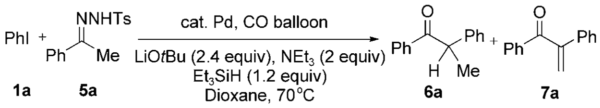
[a] Reaction conditions: **1a–i** (1.0 equiv), **2a–j** (2.0 equiv), and **3** (1.1 equiv). [b] Yield of the isolated product. [c] The product was a mixture of keto and enol. [d] No reaction.

A series of aryl iodides **1a–i** were then subjected to the optimal reaction conditions with α-diazocarbonyl compounds **2a–j**. As shown in Table 2, the corresponding 1,3-dicarbonyl products were obtained in moderate to good yields in all cases. The reaction was found to be marginally affected by the sterics of the substituents on the aryl iodides, as shown by the reaction of diazoester **2a** with *o*-iodotoluene (**1b**), which gave lower yields (Table 2, entry 2). For the scope of diazo substrates, both α-alkyl- and α-aryl-substituted substrates worked well to afford the corresponding products in good yields, except in the case when the α-aryl α-diazoacetate contains strong electron-withdrawing substituents.

Next, this palladium-catalyzed reaction was extended to diazo substrates not bearing a carbonyl substituent. These nonstabilized diazo substrates can be generated in situ from *N*-tosylhydrazones.[3b,c,4c] Therefore, phenyl iodide (**1a**) and *N*-tosylhydrazone **5a** were subjected to similar reaction conditions in the presence of LiO*t*Bu. A mixture of the expected ketone **6a** and enone **7a** (93:7) was isolated in 67% yield (Table 3, entry 1). The product **7a** results from a β-hydride elimination in the last step of catalytic cycle (see below). Additional studies revealed that both the yield and ratio of the products were drastically affected by the type of palladium catalyst (Table 3, entries 2–7). After extensive optimization,[9] two sets of reaction conditions were identified, which could afford either **6a** or **7a** selectively, both in good yields [Table 3, entry 8 (conditions **I**) and entry 9 (conditions **II**)].

With the two sets of optimized conditions, the reaction scope was examined (Table 4). Both reaction conditions **I** and **II** worked well, affording the either the ketone (**6b–e**) or the enone (**7b–e**), respectively; however, in the case of **5c** the β-

Table 3: Selected conditions of palladium-catalyzed reaction of CO with **1a** and **5a**.[a]



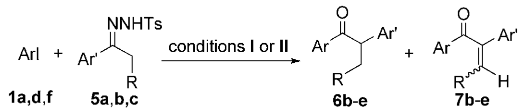
Entry	Cat. (mol%)	*t* [h]	Yield [%][b] (**6a**+**7a**)	Ratio[b] (**6a**:**7a**)
1	[Pd(PPh$_3$)$_4$] (5)	8	71 (67)[c]	93:7
2	[Pd(PPh$_3$)$_2$Cl$_2$] (5)	12	63	89:11
3	[Pd$_2$(dba)$_3$] (2.5)/dppb (5)	8	30	97:3
4	[Pd$_2$(dba)$_3$] (2.5)/[HP*n*Bu$_3$]BF$_4$ (10)	12	11	> 99:1
5	[Pd$_2$(dba)$_3$] (2.5)/P(OPh)$_3$ (10)	12	16	38:62
6	[Pd$_2$(dba)$_3$] (2.5)/P*t*Bu$_3$ (10)	12	28	< 1:99
7	[Pd$_2$(dba)$_3$] (2.5)/[HPCy$_3$]BF$_4$ (10)	12	45	31:69
8[d]	[Pd(PPh$_3$)$_4$] (5)	15	84 (76)[c]	97:3
9[e]	[Pd$_2$(dba)$_3$] (2.5)/[HPCy$_3$]BF$_4$ (10)	13	80 (71)[c]	< 1:99

[a] Reaction conditions: **1a** (1.0 equiv), and **5a** (2.0 equiv). [b] Determined by GC/MS methods. [c] Yield of isolated product given within the parentheses. [d] With 2.0 equiv of *i*Pr$_2$NH instead of NEt$_3$. [e] In the absence of Et$_3$SiH in MeCN.

hydride elimination predominated under both conditions (Table 4, entries 7 and 8).

The entire catalytic cycle of this reaction is proposed in Scheme 3.[9] The reaction is initiated by oxidative addition of Pd^0 to the aryl iodide, affording the Pd^{II} intermediate **A**. Then

Table 4: Palladium-catalyzed reaction of CO with **1a**,**d**,**f** and **5a**–**c**.



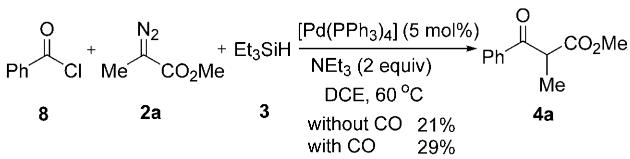
Entry[a]	1: Ar	5: Ar', R	t [h]	Yield [%][b]	Ratio (6:7)[c]
1	**1d**: p-MeOC$_6$H$_4$	**5a**: C$_6$H$_5$, H	15	85	93:7
2	**1d**: p-MeOC$_6$H$_4$	**5a**: C$_6$H$_5$, H	12	86	<1:99
3	**1f**: p-MeO$_2$CC$_6$H$_4$	**5a**: C$_6$H$_5$, H	14	56	98:2
4	**1f**: p-MeO$_2$CC$_6$H$_4$	**5a**: C$_6$H$_5$, H	12	54	<1:99
5	**1a**: C$_6$H$_5$	**5b**: 2-naph, H	15	72	96:4
6	**1a**: C$_6$H$_5$	**5b**: 2-naph, H	12	71	<1:99
7	**1a**: C$_6$H$_5$	**5c**: C$_6$H$_5$, Me	15	94	33:67[d]
8	**1a**: C$_6$H$_5$	**5c**: C$_6$H$_5$, Me	12	72	<1:99[d]

[a] For entries 1, 3, 5, and 7, the reaction was carried out under reaction conditions **I**, for entries 2, 4, 6, and 8, the reaction was carried out under reaction conditions **II**. [b] Yield of isolated **6** and **7** combined. [c] Determined by ^{1}H NMR (400 MHz) method. [d] For **7e**, $E/Z = 2:3$.

carbon monoxide insertion affords the Pd–acyl intermediate **B**. Interaction of the α-diazo compound with **B** produces palladium–carbene intermediate **C**, and migratory insertion of the acyl group into the carbenic carbon atom of the palladium–carbene generates C-bound enolate **D**, which equilibrates with the corresponding O-bound enolate **E**. In the reaction with α-diazocarbonyl compound, η^2-O, O-bound intermediate **E** (R' = COR'') is predominant, from which transmetallation with Et_3SiH and subsequent reductive elimination affords 1, 3-dicarbonyl compound as the only product. For the reaction with a nonstabilized diazo compound as a substrate, the equilibrium between **D** and **E** would be influenced by the phosphine ligands.[11] β-Hydride elimination from **D** affords enone product.

Since the possibility exists that the primary product of the reaction is a silyl enolate rather than a ketoester, we prepared silyl enolate from ketoester **4a** for comparison.[9] The silyl enolate was found to be stable to silica gel column chromatography. Careful inspection of the crude mixture of the palladium-catalyzed reaction of **1a** and **2a** under standard reaction conditions could not detect any silyl enolate. This experiment rules out the possibility of silyl enolate as primary product, which is evidence supporting the palladium hydride species **G** as the intermediate in the final step of the catalytic cycle.

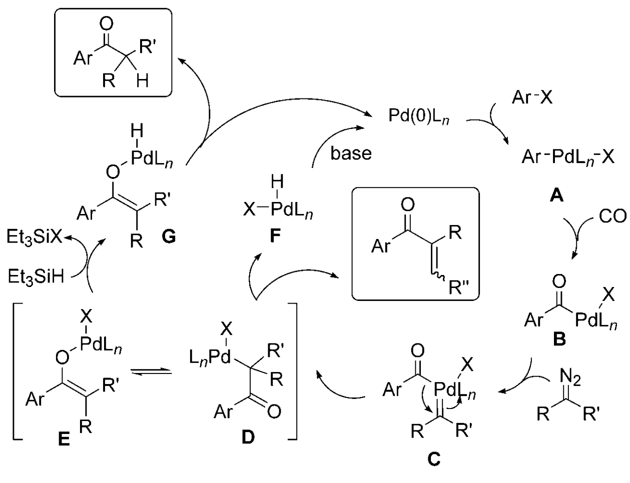
To substantiate the mechanistic rationale, we examined palladium-catalyzed reactions of methyl α-diazopropionate (**2a**) and benzoyl chloride (**8**; Scheme 4). The reaction gave



Scheme 4. Palladium-catalyzed reaction of an acyl chloride with **2a**.

the acyl group migration product **4a** in 21 % yield. In the presence of an atmosphere of CO, the yield was slightly higher. A control experiment suggests that no reaction occurs in the absence of the palladium catalyst. These results are consistent with the mechanistic rationale which involves acyl migratory insertion as the key step.

In summary, we have reported the first palladium-catalyzed tandem migratory insertion with both CO and a carbene. This reaction builds a connection between a palladium–carbene process and palladium-catalyzed carbonylation, which may open new possibilities for the exploration of the potential of palladium-catalyzed carbene transformations.



Scheme 3. Mechanistic rationale.

Experimental Section

Typical procedure for $[Pd(PPh_3)_4]$-catalyzed reactions of CO with α-diazocarbonyl compounds and aryl iodides: Under a nitrogen atmosphere, $[Pd(PPh_3)_4]$ (17.3 mg, 0.015 mmol) was added to a flame-dried round-bottomed flask. The flask was then sealed and evacuated to a vacuum of 15 mmHg, and fitted with a CO balloon. A solution of iodobenzene (**1a**; 61 mg, 0.3 mmol), methyl α-diazopropionate (**2a**; 68 mg, 0.6 mmol), triethylsilane (**3**; 38 mg, 0.33 mmol), and triethylamine (61 mg, 0.6 mmol) in 4 mL of DCE was added using a syringe. The mixture was stirred at 60 °C until **2a** disappeared as judged by TLC. The solution was removed in vacuo to yield a residue, which was purified by flash chromatography (silica gel) to afford pure **4a** as a pale yellow oil (51 mg, 88 %).

Received: November 11, 2009

Keywords: carbenes · carbonylation · diazo compounds · migratory insertion · palladium

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