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Supramolecular Pd(II) complex of DPPF and dithiolate: An efficient catalyst for amino and phenoxycarbonylation using $Co_2(CO)_8$ as sustainable C1 source

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ABSTRACT

Highly active, efficient and robust "dppf ligated tetranuclear palladium dithiolate complex" was synthesized and applied as a catalyst for chemical fixation of carbon monoxide for the synthesis value added chemicals such as tertiary amide and aromatic esters. The synthesized catalyst was characterized using different analytical techniques such as elemental analysis, ^1H and ^{31}P NMR spectroscopy. The use of $Co_2(CO)_8$ as a cheap, less toxic and low melting solid surrogate are additional advantages over the current protocol. The catalyst showed superior activity towards the Amino (10^{-3} mol % catalyst) and Phenoxycarbonylation (10^{-2} mol % catalyst) and high TON (10^4 to 10^3) and TOF (10^3 to 10^2 h^{-1}). The Betol and Lintrin (active drug molecules) were synthesized under an optimized reaction condition. The scalability of the current protocol has been demonstrated up-to the gram level.

Introduction

The development of efficient and robust methods for the synthesis of aromatic amides and esters is extremely significant in synthetic organic chemistry. Aromatic amides and esters are the most common and important structural scaffold and building blocks mainly found in organic synthesis, pharmaceutically active drug molecules and also in natural products (Fig. 1). They have been also found in agrochemicals, peptides, polymers and biologically active molecules [1–5].

Conventionally, the aromatic amides have been synthesis by (i) condensation of carboxylic acids or acyl chlorides with amines, (ii) oxidative amidation of benzaldehydes, benzyl-amine, and benzyl alcohols with amines, (iii) trans-amidation of primary amides and the aminolysis of acids or esters by coupling with secondary or tertiary amines have been also reported [6–21]. However, the aminocarbonylation of aryl halides with amines has been a most potent and robust tool in the synthetic chemistry. There are several reports available for this reaction by homogeneous as well as heterogeneous palladium systems for the synthesis of amides [22–30].

Likewise, traditionally the aromatic esters were synthesized from (i) coupling between carboxylic acids with phenol/ alcohols/ alkyl halides using lewis acids or strong bronsted acids (ii) alkylation of carboxylate salt of alkali metal, alkaline earth metals, acylation of phenol with an acyl halides or acid anhydrides has been widely studied [31–40]. Now-a-days, the palladium-catalyzed carbonylative cross-coupling reactions have emerged in the last few years as the most powerful C–C bond forming processes for the synthesis of aromatic esters [41–50].

Nowadays, the palladacycles are important, popular and thoroughly investigated class of organopalladium due to its accessible, thermal stability, and high activity at lower catalyst loading. There are several heteroatom containing (–N, –S, –P and –O) active precursors, which have been used for various cross-coupling reactions [51–60]. Typically, the higher TON and TOF were observed in non carbonylative approaches compared with carbonylative approaches. This is attributed to the π acceptor character of carbon monoxide. Carbonylation of aryl halides lies in the coordination of CO to the metal center; when bound to the palladium, the π acceptor character of CO significantly reduces the reactivity of the palladium towards oxidative insertion into the C–X bond. Sometimes, the catalytic activity leads to decreases due to the facile aggregation of palladium metal. Hence, to achieve the high TON and TOF by reducing palladium concentration (ppm level) in carbonylation is a challenging task. Literature, survey shows that

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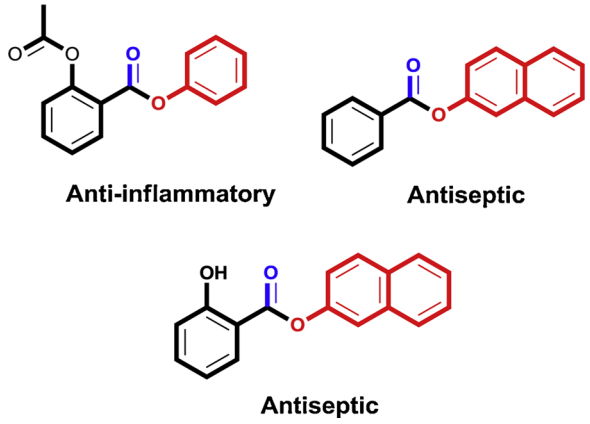


Fig. 1. Representative examples of pharmaceutically active drug molecules.

palladacycles have been seldom reports on the carbonylation to generate higher TON and TOF [61–63].

However, the cumbersome handling of CO gas hampered for its further application in academic as well as industry. Hence, recently, many researchers turned the attention towards the development of surrogate chemistry for the synthesis of amides and esters [64–69]. They have used various solid as well as liquid CO surrogates although all of these CO surrogates have their own merit still to develop such a system which works at lower metal concentration and subsequently generates high TON and TOF. Recently, our group reported dppf ligated palladacycle for the carbonylative Suzuki-Miyaura reaction using $Co_2(CO)_8$ as a C1 source to provide high TON (10^4 to 10^3) and TOF (10^2 to 10^3 h^{-1}) [70]. To continue our research interest for developing the surrogate chemistry for carbonylation reactions, further we explore this work for the Amino and Phenoxycarbonylation reactions. The concept of low catalyst loading at CO source still not been addressed for this reaction.

We have recently developed the supramolecular Pd(II) dithiolate complexes with diphosphines of varied bite angles $[Pd_2(P^{\frown}P)_2(SC_{12}H_8S)]_2(OTf)_4$ ($P^{\frown}P$: dppe (1,2-bis(diphenylphosphino) ethane); Xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthenes) and dppf (1,1′-bis(diphenylphosphino)ferrocene)). These complexes are highly soluble, stable and robust catalysts and showed excellent activity in Suzuki [59,71], Heck [60] C–C coupling reactions, and in carbonylative Suzuki-Miyaura reactions [63,70]. Next, we decided to explore the Amino and Phenoxycarbonylation reactions using $Co_2(CO)_8$ as C1 source employing the tetranuclear complex $[Pd_2(dppf)_2(SC_{12}H_8S)]_2(OTf)_4$ (Pd(1)) as a catalyst which provided high TON and TOF.

Results and discussion

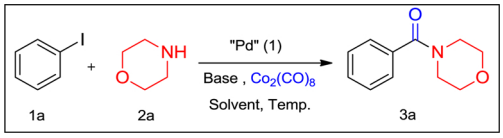
Initially the reaction optimization was carried out by carbonylative coupling between iodobenzene (**1a**) and morpholine (**2a**) led to the synthesis of amide as a model reaction. We tested various reaction optimization parameters such as CO sources, time, temperature, bases, and solvents on the model reaction and the outcomes were summarized in Table 1. Initially, we investigated commercially available "Pd" precursors for the model reaction. Here, K_2CO_3 used as a base, and toluene as a solvent along with $Co_2(CO)_8$ as C1 source and content were heated at 80 °C for 12 h. The $Pd(OAc)_2$, and $PdCl_2(PPh_3)_2$ provided moderate conversion of iodobenzene (55% and 60% respectively) and heterogeneous catalysts such as Pd/C, and Pd@GOIL (Palladium ion containing ionic liquid immobilized onto graphene oxide) provided only 35% and 45% of conversion with medium selectivity (Table 1, **entries 1-4**). Next, the same reaction proceeded with the synthesized Pd (1), and delightfully it was observed that higher conversion (78%) and selectivity (95%) than other palladium precursors (Table 1, **entry 5**). By motivated from this results further optimization was carried out with Pd(1) catalyst. To ensure the higher conversion, next we studied the effect of various inorganic as well as organic bases on the model reaction. It was observed that inorganic bases such as Na_2CO_3 and K_3PO_4 provided 73% and 82% conversion and good selectivity (Table 1, **entries 6 and 7**), while organic bases DBU and NEt_3 provided higher conversion of iodobenzene (85% and 95%) with formation of predominant species of **3a** (Table 1, **entries 8 and 9**). Hence, the base study revealed that NEt_3 is best based for this reaction. Solvents play a crucial role in the reaction hence they were screened for the model reaction. Non polar solvent like toluene (Table 1, **entry 9**) furnished excellent conversion (95%) and selectivity (100%) while use of polar solvents such as DMF (90%), THF (87%), and PEG-200 (60%) conversion of iodobenzene was noted (Table 1, **entries 10-12**). Based on these results toluene was selected for further studies. Subsequently, we studied

the effect of various CO surrogates on the model reaction (Table 1, **entries 13 and 14**). The n-formylsachharin (Table 1, **entry 13**) provided only 66% conversion with 88% selectivity and if we used phenyl formate as a C1 source it gave 70% conversion and 78% selectivity towards the product (Table 1, **entry 14**). Hence, we could conclude the conversion and selectivity provided by $Co_2(CO)_8$ was higher than other C1 sources and it choose as optimized C1 source for remaining optimization. Next, varying the reaction temperature to 100 °C, 60 °C and it was found that 80 °C to be the optimized reaction temperature (Table 1, **entry 15 and 16**). Next, after time study we noticed that at 15 h didn't have any changes in conversion and selectivity, if on reducing the reaction time to 10 h, the conversions as well as in selectivity were decreased (Table 1, **entries 17 and 18**). Hence, it was concluded at 12 h, the reaction proceeded smoothly with higher conversion and selectivity. However, in the absence of palladium catalyst reaction did not proceed which conformed the importance of the catalyst (Table 1, **entry 19**). Finally the optimized parameters are follows: 1a (0.5 mmol), 2a (0.7 mmol), Pd"1" (10^{-1} mol %), NEt_3 (1 mmol), $Co_2(CO)_8$ (0.3 mmol), toluene (4 mL), 80 °C for 12 h.

Next, we investigated the effect of catalyst loading on the aminocarbonylation reaction (Table 2). When decreasing the catalyst loading from 1 mol % to 0.001 mol % (detail process as shown in ESI), we didn't notice any changes in the conversion and yield of the product (Table 2, **entries 1-4**) with TON ranging from 9.5×10^1 to 9.3×10^4 and TOF from 0.79×10^1 to 7.75×10^3 respectively. Further, decreasing the catalyst loading to 0.0001 mol % the conversion and yield of the product were lowered (Table 2, **entry 5**). It indicated that the catalyst loading up to 0.001 mol % provided satisfactory conversion and yield of the product below that it's affected the reaction. To ensure maximum conversion and yield, next to the same reaction (0.0001 mol %) was proceeded by increasing reaction temperature to 120 °C, unfortunately, it didn't show any changes in the conversion and yield of the product (Table 2, **entry 6**). Although, TON and TOF amplified up-to (8.6×10^5) and (5.37×10^4 h^{-1}) respectively. Hence, finally we concluded that a minimum 0.001 mol % catalyst loading required for achieved maximum TON and TOF.

Next, we turned the attention towards the synthesis of various amides under the optimized reaction condition. The simple iodobenzene, *o*-Me, *p*-Me and *p*-OMe iodobenzene were smoothly reacted with morpholine and converted into amide **3a**, **3b**, **3c**, and **3d** respectively, and producing the TON ranges from 8.8×10^4 to 9.3×10^4 and TOF 7.3×10^3 to 7.5×10^3 h^{-1} (Table 3, **entries 1-4**). Further, we screened the various cyclic amines with simple and substituted iodobenzene for the synthesis of tertiary amides. Initially, the *o*-iodonaphthalene was satisfactorily converted into **3i** by coupled with diethylamine and provided catalytic TON 9.0×10^4 and TOF 7.5×10^3 h^{-1} (Table 3, **entry 9**). Next, the strong electron donating moiety such as *o*-Me, and weakly donating moiety such as *p*-fluoro iodobenzene was proficiently converted into **3j** and **3k** by carbonylation for the synthesis of amides. The results showed that the piperidine was

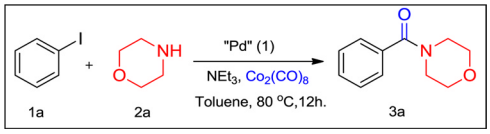
Table 1
Screening of optimal reaction condition for Aminocarbonylation.[a]



Entry No	Pd precursors	Base	Solvent	CO Source	Temp. (°C)	Time (h)	Conv.[b] (%)	Select.[b] (%)
1	$Pd(OAc)_2$	K_2CO_3	Toluene	$Co_2(CO)_8$	80	12	55	60
2	$PdCl_2(PPh_3)_2$	K_2CO_3	Toluene	$Co_2(CO)_8$	80	12	60	78
3	Pd/C	K_2CO_3	Toluene	$Co_2(CO)_8$	80	12	35	44
4	Pd@GOIL	K_2CO_3	Toluene	$Co_2(CO)_8$	80	12	45	85
5	Pd(1)	K_2CO_3	Toluene	$Co_2(CO)_8$	80	12	78	95
6	Pd(1)	Na_2CO_3	Toluene	$Co_2(CO)_8$	80	12	73	93
7	Pd(1)	K_3PO_4	Toluene	$Co_2(CO)_8$	80	12	82	96
8	Pd(1)	DBU	Toluene	$Co_2(CO)_8$	80	12	85	99
9	**Pd(1)**	**NEt_3**	**Toluene**	**$Co_2(CO)_8$**	**80**	**12**	**95**	**100**
10	Pd(1)	NEt_3	DMF	$Co_2(CO)_8$	80	12	90	95
11	Pd(1)	NEt_3	THF	$Co_2(CO)_8$	80	12	87	90
12	Pd(1)	NEt_3	PEG-200	$Co_2(CO)_8$	80	12	60	90
13	Pd(1)	NEt_3	Toluene	n-formylsachharin	80	12	66	88
14	Pd(1)	NEt_3	Toluene	Phenyl Formate	80	12	70	78
15	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	100	12	96	100
16	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	60	12	76	100
17	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	80	15	95	98
18	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	80	10	88	95
19	–	NEt_3	Toluene	$Co_2(CO)_8$	80	12	–	–

[a] Reaction condition: 1a (0.5 mmol), 2a (0.7 mmol), Pd (1) 10^{-1} mol%, base (1 mmol), CO source (0.3 mmol), solvent (4 mL).
[b] Conversion and selectivity were calculated based on GC-GCMS.

Table 2
Effect of catalyst loading on the Aminocarbonylation reaction.[a]



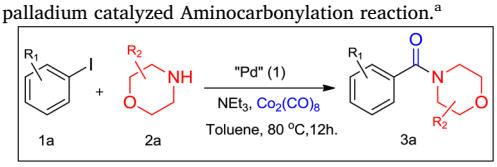
Entry No	Pd 1 (mol%)	Conv.[b] (%)	Yield[b] (%)	TON	TOF(h^{-1})
1	1	97	95	9.5×10^1	0.79×10^1
2	0.1	95	94	9.4×10^2	7.83×10^1
3	0.01	96	93	9.3×10^3	7.75×10^2
4	**0.001**	**95**	**93**	**9.3×10^4**	**7.75×10^3**
5	0.0001	90	88	8.8×10^5	7.33×10^4
6[c]	0.0001	89	87	8.7×10^5	7.25×10^4

[a] Reaction conditions: 1a (0.5 mmol), 2a (0.7 mmol), NEt_3 (1 mmol), CO source (0.3 mmol), toluene (4 mL), 80 °C, 12 h.
[b] Conversion and Yield were calculated based on GC-GCMS. [c]120 °C.

efficiently coupled with simple iodobenzene to form of **3e** with TON 9.3×10^4 and TOF 7.7×10^3 h^{-1}(Table 3, **entry 5**). Next, the pyrrolidine was successfully transformed into esters **3f**, **3g** and **3h** by carbonylative coupling with iodobenzene, *o*-bromo and *o*, *p* di-fluoro iodobenzene while generated TON ranges from 6.8×10^4 to 7.3×10^4 and TOF 6.8×10^3 to 7.3×10^3 h^{-1} (Table 3, **entries 6-8**). Then we moved towards the use of acyclic coupling with diethylamine as an amine source (Table 3, **entries 10** and **11**). The reaction produced the catalytic TON (8.2×10^4 and 8.3×10^4) and TOF (6.8×10^3 to 6.9×10^3 h^{-1}) respectively. However, aryl iodide containing strong electron withdrawing groups *p*-nitro and *o*-nitro also converted into corresponding amides of **3l** and **3m** with good yield with corresponding high TON 6.4×10^4 to 7.0×10^4 and TOF 6.4×10^3 to 5.8×10^3 h^{-1} (Table 3, **entries 12** and **13**). By motivation of the above results, next we proceeded the reaction with longer chain amines, such as dibutyl amine was carbonylative coupled with *p*-Me iodobenzene to produce **3n** with satisfactory yield and achieved catalytic TON 6.8×10^4 and TOF 5.6×10^3 h^{-1}(Table 3, **entry 14**). Delightfully, it was observed that aromatic amines such as benzyl amine also efficiently converted into **3o** by coupling with iodobenzene while they produced TON 7.3×10^4 and TOF 6.0×10^3 h^{-1} (Table 3, **entry 15**).

We initiated the reaction optimization by carbonylative cross-coupling between iodobenzene (**4a**) with phenol (**5a**) for the synthesis of ester (**6a**) as a model reaction. Various parameters like base, time, temperature were tested and summarized results are shown in Table 4. Initially, the investigation was carried out by using various commercially and synthesized palladium precursors such as $PdCl_2$, $Pd(OAc)_2$, Pd@GOIL on the model reaction at 100 °C, for 15 h (Table 4, **entries 1-3**). Here, we used NEt_3 as a base and $CO_2(CO)_8$ as a C1 source in toluene as a solvent. It was noted that conversion and selectivity were not more than 77% and 93% respectively. Gratifyingly it was observed that the excellent catalytic activity [conversion (96%) and selectivity (100%)] than rest one when the same reaction proceeded with Pd(1). By screening of palladium precursors, Pd(1) was found to be superior than other (Table 4, **entry 4**). Since, base a vital for this reaction, organic bases such as NEt_3 (96%), DBU (87%) (Table 4, **entries 4 and 5**) and inorganic bases such as K_2CO_3 (70%), and KO*t*Bu (83%) were screened but all were found to be inferior to NEt_3 and gave lower conversion and selectivity (Table 4, **entries 6 and 7**). Next, the series of solvents such as toluene, 1, 4-dioxane and THF were screened for this reaction. As shown in Table 4 reaction could not proceed smoothly in polar solvents (1, 4-dioxane, and THF) (Table 4, **entries 8 and 9**) than non-polar toluene. Excellent conversion (96%) and selectivity (100%) were achieved using toluene hence it was used for further optimization. Subsequently, we studied the effect of various CO surrogates including gaseous CO for the model reaction. It was observed that CO (balloon) provided excellent conversion and selectivity, while moderate conversion and selectivity were found when n-formylsaccharin as a C1 source (Table 4, **entries 10 and 11**). Since $Co_2(CO)_8$ would allow to use of the C1 source for this reaction, and it was chosen as the choice of CO surrogate (Table 4, **entries 4**). Further, increasing the reaction temperature (120 °C) didn't have a significant effect on conversion, while

Table 3
The substrate scope of palladium catalyzed Aminocarbonylation reaction.[a]



1 **3a** 93% TON: 9.3×10^4 TOF: 7.7×10^3	2 **3b** 89% TON: 8.9×10^4 TOF: 7.4×10^3	3 **3c** 90% TON: 9.0×10^4 TOF: 7.5×10^3	4 **3d** 88% TON: 8.8×10^4 TOF: 7.3×10^3
5 **3e** 93% TON: 9.3×10^4 TOF: 7.7×10^3	6 **3f** 85% TON: 8.5×10^4 TOF: 7.0×10^3	7 **3g** 82% TON: 8.2×10^4 TOF: 6.8×10^3	8 **3h** 88% TON: 8.8×10^4 TOF: 7.3×10^3
9 **3i** 90% TON: 9.0×10^4 TOF: 7.5×10^3	10 **3j** 82% TON: 8.2×10^4 TOF: 6.8×10^3	11 **3k** 83% TON: 8.3×10^4 TOF: 6.9×10^3	12 **3l** 77% TON: 7.7×10^4 TOF: 6.4×10^3
13 **3m** 70% TON: 7.0×10^4 TOF: 5.8×10^3	14 **3n** 68% TON: 6.8×10^4 TOF: 5.6×10^3	15 **3o** 73% TON: 7.3×10^4 TOF: 6.0×10^3	

[a]**Reaction condition**: 1a (0.5 mmol), 2a (0.7 mmol), NEt_3 (1 mmol), Pd (1) 10^{-3} mol%, $CO_2(CO)_8$ (0.3 mmol), toluene (4 mL), 80 °C, 12 h. [b]Yield was calculated based on GC-GCMS. TOF (h^{-1}).

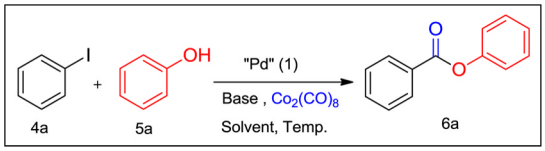
only 77% conversion was found when temperature decreases to 80 °C (Table 4, **entries 12 and 13**). Hence, it was confirmed that 100 °C temperature is required for getting higher conversion and selectivity. Further, there is no significant changes were noted when the reaction proceeded at 18 h while decreases the reaction time to 12 h and 10 h led to decreasing in conversion and selectivity (Table 4, **entries 14-16**). Hence, the time study revealed that a minimum 15 h required to getting maximum conversion and selectivity. Next, the reaction carried out without catalyst and it proceeded to 0% conversion and selectivity and which signifies the importance of the catalyst (Table 4, **entry 17**). Finally, optimized reaction parameters are follows: 4a (0.5 mmol), 5a (0.7 mmol), Pd"1" (10^{-1} mol %), NEt_3 (1.5 mmol), toluene (4 mL) at 100 °C for 15 h.

After, optimization next we turned the attention towards the decreasing the catalyst loading and its effects on phenoxycarbonylation are summarized in Table 5. Delightfully, it was observed that conversion and yield remain constant when the catalyst loading decreases from 1 mol % to 0.01 mol %. While, the reaction generated catalytic TON and TOF are 10^3 and 10^2 respectively (Table 5, **entries 1-3**).

Further, the conversion and yield were significantly decreased, when palladium concentration lowered to 0.001 mol %, (Table 5, **entry 4**). Although, high TON 8.7×10^4 and TOF $5.80\times10^3\,h^{-1}$ was achieved. Next, the same reaction by increasing the temperature to 120 °C for 15 h and it was noted that no temperature effect was observed on conversion and yield of the product (Table 5, **entry 5**). The TON 8.8×10^4 and TOF $5.86\times10^3\,h^{-1}$ were achieved. Hence, finally we conclude that 0.001 mol % palladium concentration is sufficient for maximum TON and TOF.

Optimized reaction condition in hand next we explored the synthetic versatility of current protocol for the preparation of a wide variety of aromatic esters. The outcomes revealed that the reaction was progressed easily with a tolerance of a variety of functional groups and the results are summarized in Table 6. Simple iodobenzene smoothly coupled with phenol to provide the excellent yield of the **6a** and generated TON 9.3×10^3 and TOF $6.20\times10^2\,h^{-1}$ (Table 6, **entry 1**). The introduction of strong electron donating moiety such as methyl and methoxy at para position of iodobenzene gave the satisfactory yield of esters **6b** and **6c** and with corresponding TON ranging from 9.3×10^3 to 9.1×10^3 and TOF from 6.20×10^2 to $6.06\times10^2\,h^{-1}$ (Table 5, **entries 2 and 3**). However, the electron rich moiety on both iodobenzene as well as phenol (*p*-OMe and *p*-Me) were tolerated and resulted yield of ester **6d** with TON values 8.8×10^3 and TOF

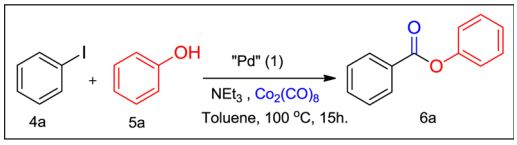
Table 4
Screening of optimal reaction condition for Phenoxycarbonylation.[a]



Entry No	Pd precursors	Base	Solvent	CO Sources	Temp.°C	Time (h)	Conv.[b] (%)	Select.[b] (%)
1	$PdCl_2$	NEt_3	Toluene	$Co_2(CO)_8$	100	15	50	83
2	$Pd(OAc)_2$	NEt_3	Toluene	$Co_2(CO)_8$	100	15	73	88
3	Pd@GOIL	NEt_3	Toluene	$Co_2(CO)_8$	100	15	77	93
4	**Pd(1)**	**NEt_3**	**Toluene**	**$Co_2(CO)_8$**	**100**	**15**	**96**	**100**
5	Pd(1)	DBU	Toluene	$Co_2(CO)_8$	100	15	87	100
6	Pd(1)	K_2CO_3	Toluene	$Co_2(CO)_8$	100	15	70	87
7	Pd(1)	KotBu	Toluene	$Co_2(CO)_8$	100	15	83	95
8	Pd(1)	NEt_3	1, 4-dioxane	$Co_2(CO)_8$	100	15	73	90
9	Pd(1)	NEt_3	THF	$Co_2(CO)_8$	100	15	77	88
10	Pd(1)	NEt_3	Toluene	CO (balloon)	100	15	95	99
11	Pd(1)	NEt_3	Toluene	n-formylsaccharin	100	15	80	92
12	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	120	15	96	100
13	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	80	15	77	99
14	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	100	18	97	100
15	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	100	12	88	100
16	Pd(1)	NEt_3	Toluene	$Co_2(CO)_8$	100	10	65	95
17	–	NEt_3	Toluene	$Co_2(CO)_8$	100	15	–	–

[a] Reaction condition: 4a (0.5 mmol), 5a (0.7 mmol), Catalyst (1) 10^{-1} mol%, CO source (0.3 mmol), Base (1.5 mmol), Solvent (4 mL).
[b] Conversion and selectivity were calculated by GC-GCMS.

Table 5
Effect of catalyst loading on the phenoxycarbonylation.[a]



Entry No	Pd (mol%)	Conv.[b] (%)	Yield[b] (%)	TON	TOF(h^{-1})
1	1	96	95	9.5×10^1	0.63×10^1
2	0.1	96	93	9.3×10^2	6.20×10^1
3	**0.01**	**95**	**93**	$\mathbf{9.3 \times 10^3}$	$\mathbf{6.20 \times 10^2}$
4	0.001	90	87	8.7×10^4	5.80×10^3
5[c]	0.001	89	88	8.8×10^4	5.86×10^3

[a] Reaction condition: 4a (0.5 mmol), 5a (0.7 mmol), NEt_3 (1.5 mmol), CO source (0.3 mmol), toluene (4 mL), 100 °C, 15 h.
[b] Conversion and Yield were calculated based on GC-GCMS.
[c] 120 °C.

$5.86 \times 10^2\ h^{-1}$ (Table 6, **entry 4**). Next, the electron withdrawing functionalities such as *p*-CN and *m*-NO_2 present on iodobenzene slightly affected the reaction and converted esters **6e** and **6f** in good yield and corresponding TON ranging from 8.0×10^3 to 8.4×10^3 and TOF 5.33×10^2 to $5.6 \times 10^2\ h^{-1}$ (Table 6, **entries 5 and 6**). Subsequently, we investigated the coupling of substituted phenol with aryl iodides for the synthesis of esters. The simple methyl substituted phenols such as *o*-Me, *p*-Me and *m*-Me are smoothly carbonylatively coupled with iodobenzene and gets converted into esters **6 g**, **6 h** and **6i** with excellent yields. It was observed that the yield of ortho substituted phenol slightly affected than the yield of meta and para substituted phenols due to the sterically hindrance of *o*-Me group. However, they provided TON ranging from 8.5×10^3 to 9.0×10^3 and TOF 5.66×10^2 to $6.0 \times 10^2\ h^{-1}$ (Table 6, **entries 7-9**). Further, the Guaiacol (ortho methoxy phenol) was smoothly converted into ester **6j** by carbonylative coupling with iodobenzene with TON values 8.3×10^3 and TOF values $5.53 \times 10^2\ h^{-1}$ (Table 6, **entry 10**). Further, the halogenated biaryl ketone such as **6k** was successfully synthesized by coupling with simple iodobenzene with 2 4-difluoro phenol. The catalytic TON 7.0×10^3 and TOF $4.66 \times 10^2\ h^{-1}$ were achieved (Table 6, **entry 11**). Finally, the strong electron withdrawing moiety such as *p*-NO_2 was tested with iodobenzene and it was observed that significant loss in the yield of **6 l** and while catalytic TON 5.0×10^3 and TOF $3.33 \times 10^2\ h^{-1}$ were achieved (Table 6, **entry 12**).

The developed synthetic methodology was then attempted for the gram-scale synthesis of amides. For this purpose next we carried out reaction of iodobenzene (5 mmol) with morpholine (7 mmol) using triethylamine (10 mmol) as a base and $Co_2(CO)_8$ as C1 source. Gratifyingly, it was found that 65% yield of desired amine (Scheme 1).

Next, we have synthesized the pharmaceutically active drug molecules under optimized reaction conditions. The active drugs such as betol (69%) and lintrin (73%) were successfully synthesized by carbonylative coupling between *o*-iodo phenol and iodobenzene with β-naphthol with an excellent yield of the products (Scheme 2).

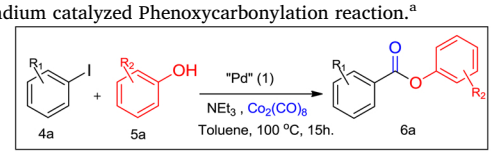
Based on previous reports [43,70] and experimental data herein we have proposed a plausible reaction mechanism of the current protocol. Initially, aryl iodide (**A**) undergoes oxidative addition (through the breaking of weak C–I bond) to the palladium atom to the formation of species (**B**). Other hand, at 80 °C the $Co_2(CO)_8$ release the CO (gas) and it gets inserted between species (**B**) to the formation of active species (**C**). Next, in the presence of base, amine undergoes transmetallation with **C** to give species **D**. Subsequently, reductive elimination of species **D** to the formation of the expected product of amide was observed (Fig. 2).

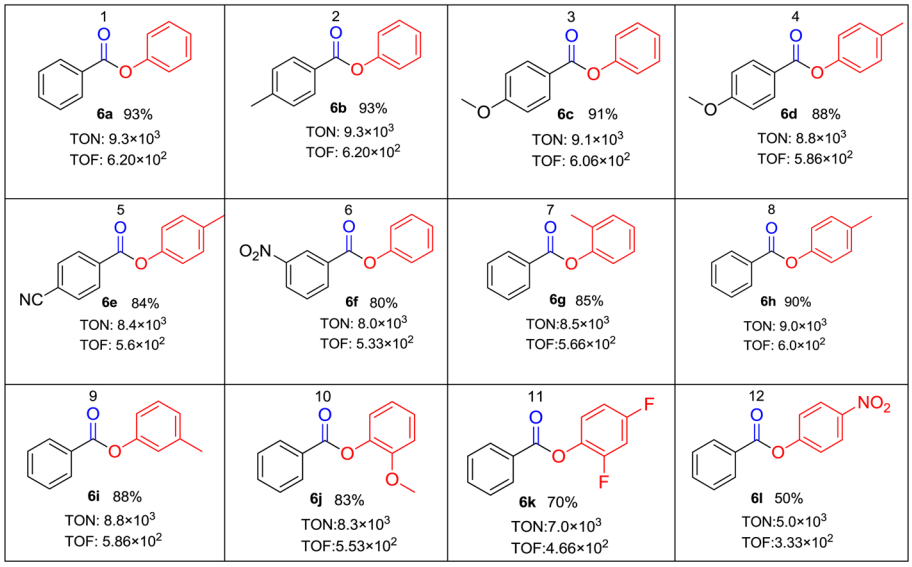
The similar reaction mechanism was observed in the Phenoxycarbonylation, however at 100 °C cobalt carbonyl released the CO and gets inserted to the formation of species C (Fig. 3).

Conclusion

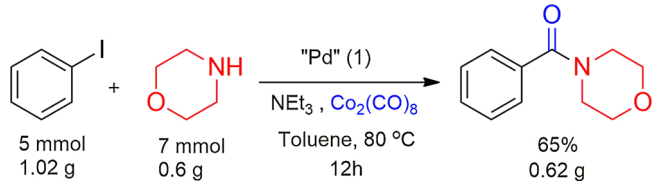
In conclusion, we have first time established methodology for amino and phenoxycarbonylation using $Co_2(CO)_8$ as C1 source instead of gaseous CO with high TON and TOF. Use of $Co_2(CO)_8$ as less toxic and inexpensive C1 source than other C1 precursors. Developed

Table 6
Substrate scope of Palladium catalyzed Phenoxycarbonylation reaction.[a]

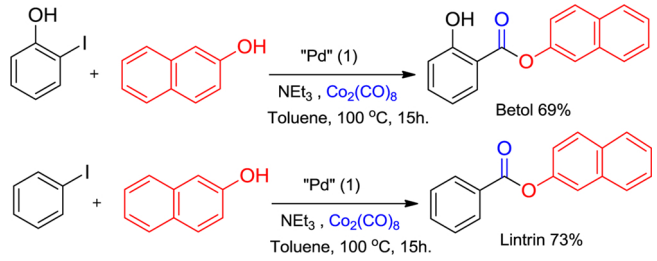




[a]**Reaction condition**: 4a (0.5 mmol), 5a (0.7 mmol), NEt_3 (1.5 mmol), Pd(1) 10^{-2} mol%, CO source (0.3 mmol), toluene (4 mL), 100 °C, 15 h. [b] Yield was calculated based on GC-GCMS. TOF(h^{-1}).



Scheme 1. Palladium catalyzed gram scale synthesis of esters using $Co_2(CO)_8$ as a C1 source.



Scheme 2. Synthesis of active drug molecules by carbonylation using $Co_2(CO)_8$ as C1 source.

methodology does not require any external additive, ligands and co-catalyst even at CO surrogate. The synthesis of amides and esters was achieved at very low catalyst loading (10^{-3} mol %) for Aminocarbonylation and (10^{-2} mol %) for Phenoxycarbonylation. The generated TON ranges from 10^4 to 10^3 and TOF from 10^3 to 10^2 h^{-1}. The practical applicability of current protocol up-to gram level and also tolerated of a wide variety of functional groups. The drug molecules Betol and Lintrin were synthesized under the optimized reaction condition. The synthesized catalyst was characterized using various analytical techniques such as CHNS, melting point, ^1H NMR and ^{31}P NMR, spectroscopy (see ESI).

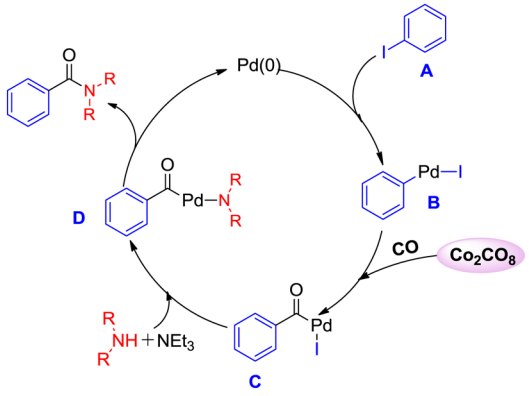


Fig. 2. Plausible reaction mechanism of the Aminocarbonylation reaction.

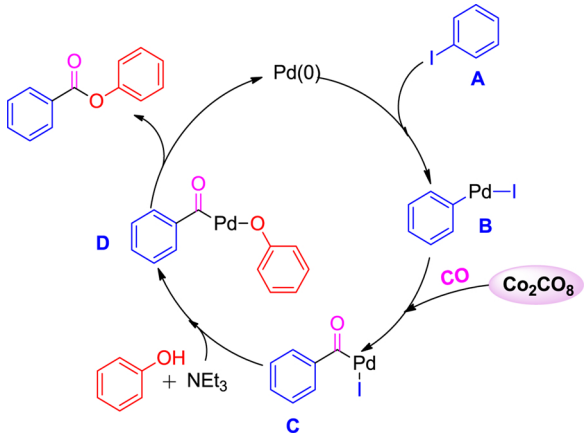


Fig. 3. Plausible reaction mechanism of Phenoxycarbonylation reaction.

Declaration of Competing Interest

This work has been checked with Ithenticate software for the plagiarism. All the data of this manuscript have been collected from our lab and this work is completely submitted in Molecular Catalysis. Submission of an article implies that the work described has not been published previously that it is not under consideration for publication elsewhere.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2019.110672.

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