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An Efficient Protocol to Synthesize N-Acyl-Enamides and -Imines *via* Pd-catalyzed Carbonylations

Lin Wang, [a] Helfried Neumann, [a] Anke Spannenberg [a] and Matthias Beller*[a]

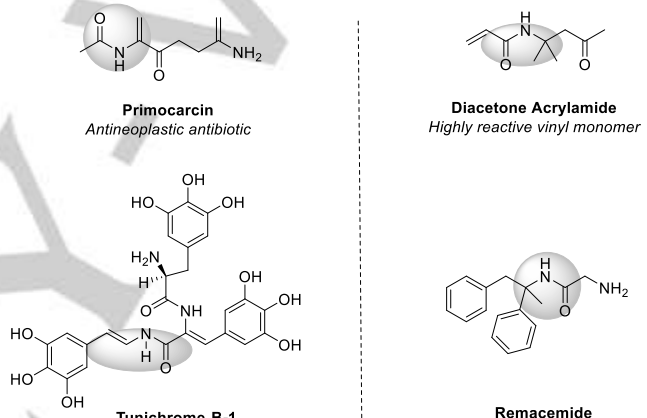
Abstract: For the first time, the bidentate phosphinite ligand 1,2-bis(di-*tert*-butylphosphinoxy)ethane ($^tBu_2POCH_2CH_2OP^tBu_2$) was synthesized. In the presence of this ligand, various N-acyl enamides were obtained in good yields and chemoselectivity *via* Pd-catalyzed carbonylation reaction of imines containing α-H. Meanwhile, imines without α-H could be transformed to N-acyl imines, which form highly hindered amides by straightforward addition of Grignard reagents.

Introduction

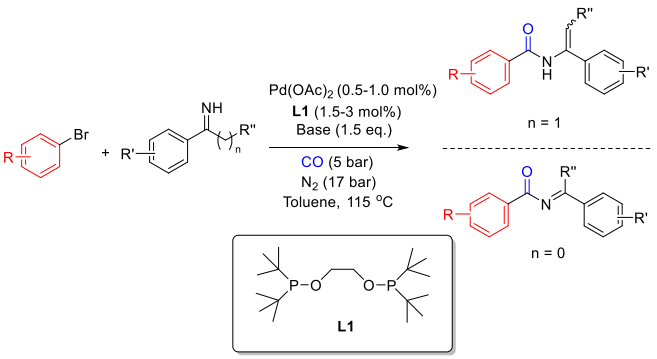
The selective generation of amide bonds is one of the most important methodologies for the synthesis of pharmaceuticals and bio-active compounds and continues to attract the interest of synthetic chemists.[1] Traditional protocols which are based on the condensation of amines and activated carboxylic acids have been proven to be efficient and are popular; however, it is undeniable that this approach suffers from limitations, e.g. necessity of coupling agents and waste formation.[2] Therefore, alternative protocols have been developed to overcome these shortcomings.[3] Nevertheless, problems still exist for the synthesis of special but useful amides such as N-acyl-enamides and related -imines.[4] N-Acyl enamides and their derivatives are versatile and powerful building blocks in organic synthesis, especially for the enantioselective hydrogenation.[5] Moreover, N-acyl enamide moieties are integral part in various natural products and pharmaceutical lead compounds (Scheme 1, left).[6] As for N-acyl imines, they constitute precursors of amides and can be used to synthesize sterically hindered derivatives – another useful unit in drug molecules and industrial products (Scheme 1, right).[7]

The palladium-catalyzed carbonylation of aryl halides allows to effectively introduce carbonyl groups into (hetero)arenes[8], which has been applied extensively to produce amides as well. Generally, it is crucial for Pd-catalyzed carbonylation reactions of less reactive aryl bromides and chlorides to control and adjust the reactivity of the active catalyst species.[9] In this respect, the development of "economical" but highly-efficient ligands is of significant importance. Although phosphines are the most common ligands for Pd-catalyzed coupling reactions[10], phosphinite ligands (R'R''POR, R, R' and R'' = alkyl or aryl group), which are easier-prepared, might be a suitable choice, too.[11] Previously, the good properties of especially bidentate phosphines were demonstrated in aryl halide carbonylations.[12] Hence, these works inspired us to develop more-economical diphosphinites.

Scheme 1. The N-acyl enamide moieties (left) and sterically hindered amide moieties (right) in chemical products



Herein, we report for the first time the synthesis of the bidentate 1,2-bis(di-*tert*-butylphosphinoxy)ethane ($^tBu_2POCH_2$-$CH_2OP^tBu_2$) ligand and its application in Pd-catalyzed carbonylations of primary imines. Compared to other common ligands, the new phosphinite allows the selective formation of the corresponding N-acyl-enamides and related –imines (Scheme 2).



Scheme 2. Pd/**L1**-catalyzed carbonylation of primary imines.

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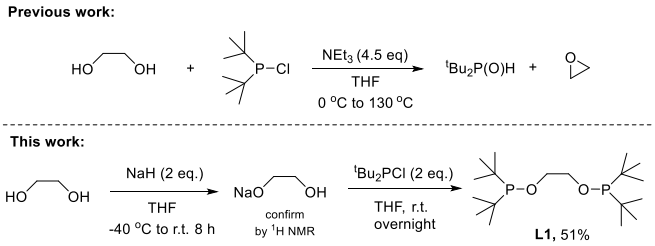
Results and Discussion

The synthesis of 1,2-bis(di-*tert*-butylphosphinoxy)ethane (L1)

Recently, we demonstrated the usefulness of monodentate di-*tert*-butylphosphinite ligands for the synthesis of aryl esters.[13] Based on that work we tried to prepare **L1** as a stable dppb-analogue. However, to the best of our knowledge this ligand has not been synthesized successfully before. Indeed, Baldwin and Fink showed that the reaction of di-*tert*-butylchlorophosphine (tBu_2PCl) with ethylene glycol gave mainly the phosphine oxide [$tBu_2PH(O)$] rather than **L1** (Scheme 3, top).[14] It is believed that steric hindrance of the *tert*-butyl groups affects the reaction negatively.



Scheme 3. Synthesis of 1,2-bis(di-*tert*-butylphosphinoxy)ethane (**L1**).

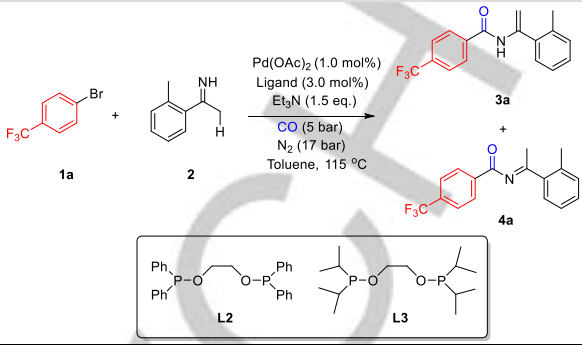
In order to improve the reaction with ethylene glycol, sodium hydride (NaH) was used to form monosodium ethylene glycolate and then tBu_2PCl was added dropwise into this slurry. As a result, **L1** was obtained in 51% yield after overnight stirring (Scheme 3, bottom). In the ^1H NMR spectrum, the signal of the *tert*-butyl group appears at 1.13 ppm as a doublet with $J^3_{H,P} = 12$ Hz) while the one of the methylene groups is found at 3.88 ppm. The singlet in the ^{31}P $\{^1H\}$ spectrum appears at 163.2 ppm, which indicates the chemical identity of the two phosphorus atoms.

Pd-catalyzed carbonylation of imines with α-H

Initially, the catalytic carbonylation of 4-(trifluoromethyl)bromobenzene (**1a**) with 1-(2-methylphenyl)-ethan-1-imine (**2**) was performed using different ligands (Table 1). In general, mixtures of the corresponding N-acyl enamide **3a** and N-acyl imine **4a** are formed. In the presence of the new ligand **L1**, N-[1-(2-methylphenyl)ethenyl]-4-trifluoromethylbenzamide (**3a**) was obtained as the only product in 83% yield and no traces of **4a** were detected (Table 1, entry 1). Other common bidentate phosphine ligands such as dppb and dppf and two bidentate phosphinite ligands **L2** and **L3** gave under similar conditions both lower conversion and mixtures of products (Table 1, entries 2-5).

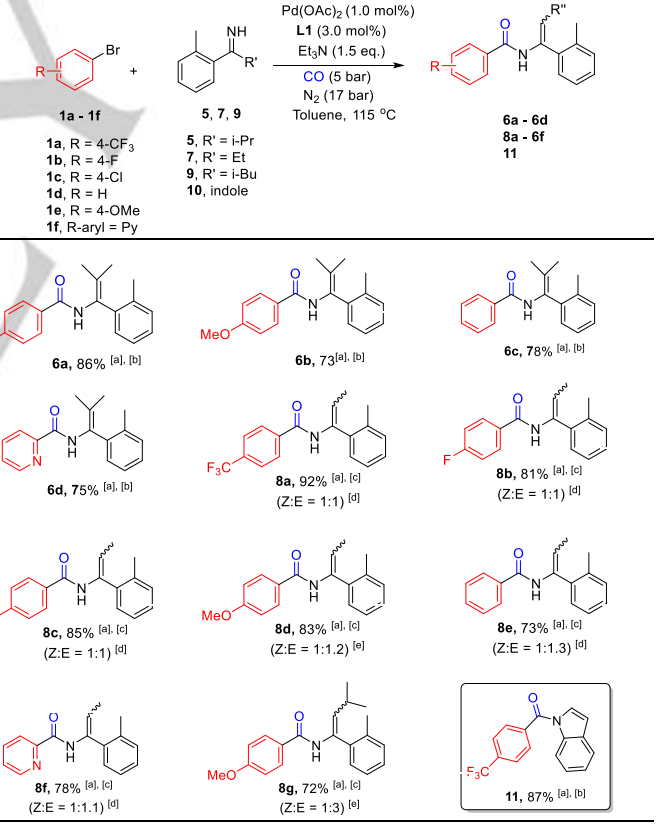
Next, we investigated the scope and limitation of this protocol using three different imines and six aryl bromides. As shown in Scheme 4 the sterically hindered N-acyl enamide **6a** was produced in good yield (86%). Both electron-rich aryl and heteraryl bromides gave good yields of the corresponding products (73% (**6b**), 78% (**6c**) and 75% (**6d**), respectively).

Table 1. The influence of different ligands on Pd-catalyzed carbonylation of 1-(2-methylphenyl)-ethan-1-imine (**2**).[a]



Entry	Ligand	Conv. (%)[b]	Yield of **3a** (%)[c]	Yield of **4a** (%)[b]
1	**L1**	83	83	0
2	dppb	30	21	9
3	dppf	70	52	15
4	**L2**	35	28	7
5	**L3**	44	32	9

[a] Reaction conditions: 1.2 mmol (4-trifluoromethyl)bromobenzene (**1a**), 1.0 mmol 1-(2-methylphenyl)-ethan-1-imine (**2**), 0.01 mmol $Pd(OAc)_2$, 0.03 mmol ligand, 1.5 mmol Et_3N, 5 bar CO, 17 bar N_2, 1.5 mL toluene, 115 °C, 18 h; [b] determined by GC, hexadecane as standard; [c] isolated yield.



[a] Reaction conditions: 1.2 mmol (hetero)aryl bromide, 1.0 mmol imine, 0.01 mmol $Pd(OAc)_2$, 0.03 mmol **L1**, 1.5 mmol Et_3N, 5 bar CO, 17 bar N_2, 1.5 mL toluene, 115 °C, 18 h; [b] isolated yield; [c] total yield. [(Z)-isomer+(E)-isomer]; [d] ratio of isolated yields of (Z)-isomer to (E)-isomer; [e] determined by ^1H NMR spectrum.

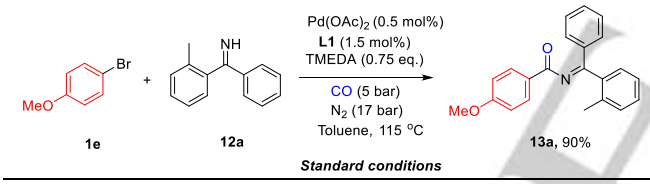
Scheme 4. Pd-catalyzed carbonylation reaction of different (hetero)aryl bromides with N-H imines with α-H.

On the other hand, when 1-(2-methylphenyl)-propan-1-imine **7** was used as substrate in this reaction, a mixture of two stereoisomers **8a** was produced in a total yield of 92% [(Z):(E) = 1:1]. Comparing different aryl bromides in this reaction, we found that electron-rich derivatives enhanced the selectivity of E-isomers slightly (**8d** and **8e**). Using an imine substrate with a sterically demanding substituent at the β-position of the alkyl group (**9**), **8g** was obtained with the (E)-isomer as the major product (75% selectivity). Finally, indole can be carbonylated in a similar manner and N-benzoylindole **11** was produced in 87% yield.

Pd-catalyzed carbonylation of imines without α-H

The novel catalyst system permits the smooth carbonylation of imines with as well as without α-H. In case of the latter substrates, obviously no formation of enamides is possible, and thus the corresponding N-acyl imines are obtained. After screening different conditions for the reaction of 4-bromoanisole (**1e**) with (2-methylphenyl)(phenyl)methanimine (**12a**) and CO, we observed optimal product yields for **13a** at lower catalyst loading in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) as base (Table 2). Interestingly, the use of stronger bases decreased the formation of products. Similarly, higher pressure of CO also lowered the yield of **13a**.

Table 2. Pd-catalyzed carbonylation of 2-methyl-α-phenyl-benzenemethanimine (**12**) under different conditions. [a]

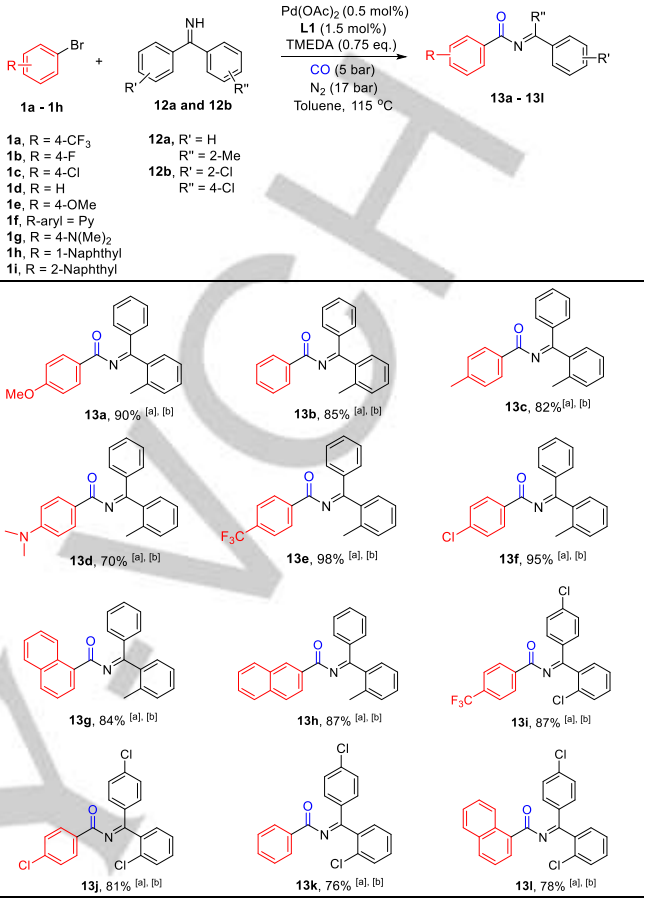


1e **12a** ***Standard conditions*** **13a**, 90%

Entry	Variation from standard conditions	Yield of **13a** (%)[b]
1	1 mol% $Pd(OAc)_2$ and 3 mol% **L1** were loaded	91
2	1.5 equiv. Et_3N instead of 0.75 equiv. TMEDA	84
3	1.5 equiv. DBU instead of 0.75 equiv. TMEDA	38
4	1.5 equiv. KO^{t}Bu instead of 0.75 equiv. TMEDA	15
5	10 bar CO instead of 5 bar CO, no N_2	76
6	20 bar CO instead of 5 bar CO, no N_2	34

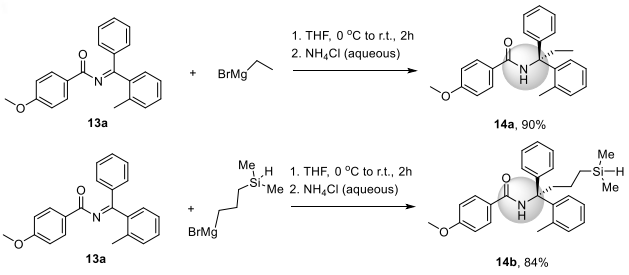
[a] Standard reaction conditions: 1.2 mmol 4-bromoanisole (**1e**), 1.0 mmol 2-methyl-α-phenyl-benzenemethanimine (**12a**), 0.005 mmol $Pd(OAc)_2$, 0.015 mmol **L1**, 0.75 mmol TMEDA, 5 bar CO, 17 bar N_2, 1.5 mL toluene, 115 °C, 18 h. [b] Isolated yield.

As shown in Scheme 5, high yields were observed for the reactions of various aryl bromides such as 4-bromotoluene, 4-bromo-N,N-dimethylaniline, 4-bromo-chlorobenzene, etc. In general, electron-withdrawing substituents (4-CF_3- and 4-Cl-) led to a higher yield (98% (**13e**) and 95% (**13f**), respectively) compared to electron-donating groups (e.g. 4-Me- and 4-$N(Me)_2$-; 82% (**13c**) and 70% (**13d**), respectively). Meanwhile, variation of the imine (**12a-b**) influenced the yield of the N-acyl imines (**13i – 13l**) only slightly.



[a] Reaction conditions: 1.2 mmol aryl bromide, 1.0 mmol imine, 0.005 mmol $Pd(OAc)_2$, 0.015 mmol **L1**, 0.75 mmol TMEDA, 5 bar CO, 17 bar N_2, 1.5 mL toluene, 115 °C, 18 h; [b] isolated yield.

Scheme 5. Pd-catalyzed carbonylation of (hetero)aryl bromides with N-H imines without α-H.

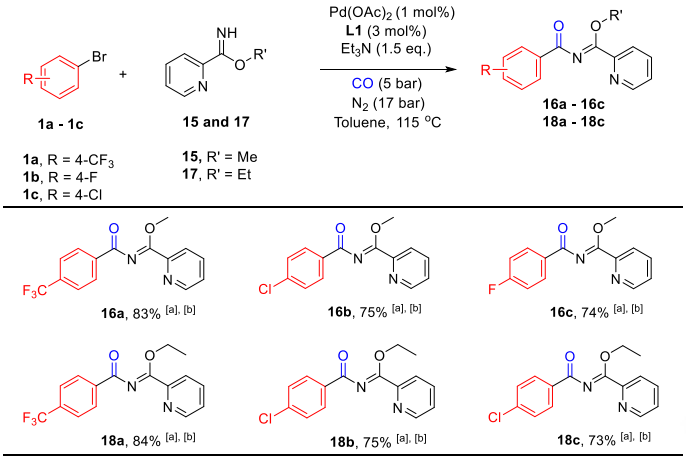


Scheme 6. Synthesis of sterically hindered amides from N-acyl imines

An important synthetic application of N-acyl imines is the preparation of highly hindered amides, which is otherwise still challenging.[15] Due to the electron-withdrawing effect of the acyl group, the imine is activated, and addition of nucleophilic Grignard reagents proceeds rapidly. For example, reaction of **13a** with two Grignard reagents yielded the corresponding amines (Scheme 6, **14a** and **14b**). Notably, the Si-H bond remained untouched by this method.

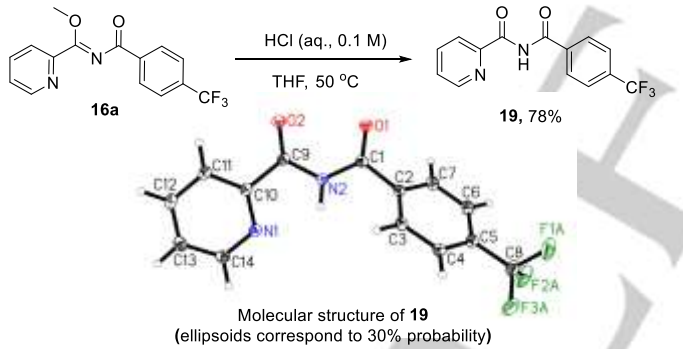
Finally, the carbonylation of related aromatic imidates [ArC(=NH)OR] was investigated. Although N-acylimidates constitute important precursors for synthesis of triazoles, diacid

anilides and their derivatives, the methods to prepare these ponderable compounds are still limited.[16] Hence, imidates **15** and **17** were smoothly converted to corresponding acyl derivatives via Pd-catalyzed carbonylation, in the presence of NEt_3 as base. The yields of products ranked from 73% to 85% (Scheme 7, **16a** – **16c**; **18a** – **18c**). Moreover, the N-acyl imidate **16a** could be converted to diacid anilides (**19**) readily through hydrolysis of N-acylimidate (**16a**) by water (Scheme 8). [17], [18]



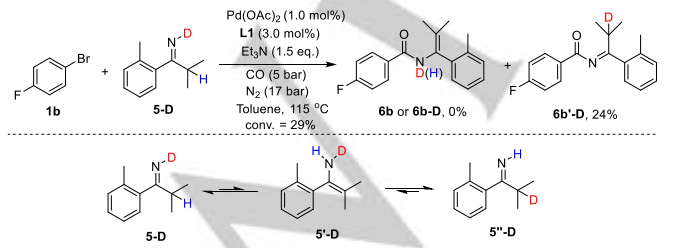
[a] Reaction conditions: 1.2 mmol aryl bromide, 1.0 mmol imidate, 0.01 mmol $Pd(OAc)_2$, 0.03 mmol **L1**, 0.75 mmol Et_3N, 5 bar CO, 17 bar N_2, 1.5 mL toluene, 115 °C, 18 h; [b] Isolated yield.

Scheme 7. Pd-catalyzed carbonylation of aromatic imidates with CO.



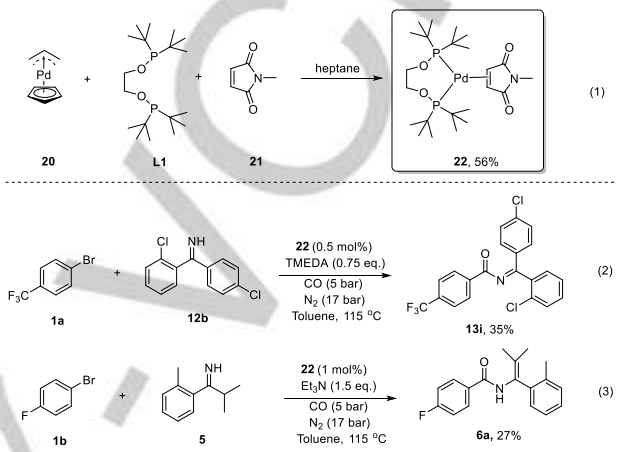
Scheme 8. Synthesis of diacid anilides **19** by hydrolysis of N-acyl imidate **16a**.

Mechanistic investigations



Scheme 9. Isotopic experiment for Pd-catalyzed carbonylation of imine.

Firstly, an isotopic experiment was explored to trace the proton of imine group (Scheme 9). Deuterated imine **5-D** was prepared and then used into the palladium catalyzed carbonylation of **1b** under the standard conditions. Consequently, the reaction resulted in a low conversion and the deuterated N-acyl imines (**6b'-D**) rather than N-acyl enamide (**6b** or **6b-D**) was produced in the yield of 24%. This interesting phenomenon indicates that: 1) In a small extent, **5b-D** could be tautomerized into **5b''-D** which shows similar property to the imine without α-H; 2) enamine intermediate **5b'-D** cannot react as nucleophile for generation of corresponding N-acyl enamide (Scheme 9).



Scheme 10. Stoichiometric reaction of Pd(allyl)(Cp) (**20**), **L1** and NMM (**21**); Carbonylation of **12b** and **5** catalyzed by palladium complex **22**. Reaction conditions: (1) 0.816 mmol **20**, 0.866 mmol **L1** and 0.816 mmol **21** in 4 mL heptane under ambient temperature overnight, **22** was obtained as pale yellow crystals in the isolated yield of 56%; (2) 1.2 mmol **1a**, 1.0 mmol **12b**, 0.005 mmol **22**, 0.75 mmol TMEDA, 5 bar CO, 17 bar N_2, 1.5 mL toluene, 115 °C, 18 h. **13i** was obtained in the isolated yield of 35%; (3) 1.2 mmol **1b**, 1.0 mmol **5**, 0.01 mmol **22**, 1.5 mmol Et_3N, 5 bar CO, 17 bar N_2, 1.5 mL toluene, 115 °C, 18 h, **6a** was obtained in the isolated yield of 27%. NMM = N-methylmaleimide.

Subsequently, the key intermediate of catalytic cycle was researched. Pd(**L1**)(NMM) (**22**) was obtained in the yield of 56% by combining Pd(allyl)(Cp) (**20**) with **L1** and N-methylmaleimide (Scheme 10, Eq. (1)). NMR (^1H, ^{31}P and ^{13}C) investigations and X-ray diffraction analysis unveiled the structure. Although the crystals of **22** suffered from poor quality, the connectivity of the molecule in which two phosphorus atoms of **L1** coordinate to the same metal center could be confirmed (see Supporting Information, Figure S4). In addition, $^{31}P\{^1H\}$ spectrum shows only one signal at 186.43 ppm, which provides another powerful evidence for the coordination mode. In the presence of **22** as catalyst, the benchmark carbonlyation reactions were performed. Equation (2) and (3) in scheme 10 demonstrate that the desired products were obtained in lower yields (35% for **13i** and 27% for **6a**, respectively), which implies that Pd^0**L1** may be the active intermediate in the catalytic cycle while NMM occupies the vacant site and lowers the reactivity of catalyst.

Conclusions

In summary, we have synthesized the bidentate phosphinite ligand 1,2-bis(di-*tert*-butyl-phosphinoxy)ethane ($^tBu_2POCH_2CH_2$-

OP^tBu_2) for the first time, which showed excellent reactivity for Pd-catalyzed carbonylations of imines. On the one hand, imines containing α-H were converted to N-acyl enamides selectively. On the other hand, aryl-imines and imidates without α-H were transformed to the corresponding N-acyl –imines and -imidates in good yields.

Experimental Section

Synthesis of 1,2-bis(di-*tert*-butylphosphinoxy)ethane (L1)

NaH (17.2 mmol, 0.42 g) and THF (30 mL) were added into a 100 mL Schlenk equipped with magnetic stirring bar. At -40 °C, ethylene glycol (7.15 mmol, 0.44 g) was added into the slurry slowly. After finishing adding, the mixture was allowed to warm to room temperature and be kept stirring for 8 h. Then the mixture was cooled to 0 °C and $^tBu_2PCl$ (14.3 mmol, 2.6 g) was added into the mixture dropwise at the same temperature. The reaction was stirred at room temperature overnight. Subsequently, THF was removed under reduced pressure followed by addition of diethyl ether (30 mL) to precipitate salt. After filtration and removal of solvents, **L1** was obtained by reduced pressure distillation (0.04 mbar, 84 – 85 °C). Yield: 51%, 1.3 g. ^{1}H NMR (300MHz, C_6D_6, ppm): δ 1.13 (d, $J^3_{H,P}$ = 12 Hz, 36H, C(C*H*$_3$)$_3$), 3.88 (m, 4H, OC*H*$_2$C*H*$_2$O); $^{31}P\{^1H\}$ NMR (121.5 MHz, C_6D_6, ppm): δ 163.2 (s); $^{13}C\{^1H\}$ NMR (75 MHz, C_6D_6, ppm): δ 27.24 ($J^2_{C,P}$ = 15.8 Hz, C(*C*H$_3$)$_3$), 34.91 ($J^1_{C,P}$ = 25.5 Hz, C(*C*H$_3$)$_3$), 73.64 (q, $J^2_{C,P}$ = 21.0 Hz, $J^3_{C,P}$ = 8.2 Hz, OCH$_2$*C*H$_2$O).

General procedure for synthesis of N-acyl enamides

To a vial (12 mL reaction volume) which was charged with $Pd(AcO)_2$ (2.2 mg, 0.01 mmol) and equipped with a septum, a small cannula and a stirring bar, **L1** (10.5 mg, 0.03 mmol), toluene (1.5 mL), Et_3N (0.21 mL), imine (1 mmol) were added. After addition of corresponding aryl bromide (1.2 mmol), the vials were placed in an alloy plate which was transferred to a 300 mL autoclave (4560 series from Parr Instruments®) under an argon atmosphere. The autoclave was flushed three times with CO and then pressurized to 5 bar CO and 17 bar N_2. The reaction was kept stirring at 115 °C for 18 h. After cooling down to room temperature, CO was released carefully. Hexadecane (226.0 mg, 1 mmol), the internal standard, was injected into reaction vials and the mixture was stirred for 10 min. The sample was analyzed by GC to determine the conversion and yield. Pure product could be obtained by column chromatography on silica gel (general eluent: hexane/ethylacetate = 6:1).

For **8a** – **8g**, which exist with two isomers, some of them (**8c**, **8e** and **8f**) were isolated into two pure isomers while some of them were obtained as a mixture of isomers. For the former, the ratio of isomers is determined by isolated yield; for the latter, the ratio of isomers is determined by ^{1}H NMR spectra.

Spectra data for selected N-acyl enamides

3a. Yield: 83%, 0.25 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 2.32 (s, 3H, Ar-C*H*$_3$), 4.30 (d, $J_{H,N(H)}$ = 1.2 Hz, 1H, C=C*H*), 6.17 (s, 1H, C=C*H*), 7.11–7.26 (m, 5H, Ar-*H* and N-*H*), 7.61 (d, $J^3_{H,H}$ = 6.0 Hz, 2H, Ar-*H*), 7.78 (d, $J^3_{H,H}$ = 6.0 Hz, 2H, Ar-*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm): δ 19.69 (*C*H$_3$), 104.03 (C=C), 123.56 ($J^1_{C,F}$ = 270.8 Hz, -*C*F$_3$), 125.75 ($J^3_{C,F}$ = 3.8 Hz, *C*$_{Ar}$), 125.85 ($J^3_{C,F}$ = 3.8 Hz, *C*$_{Ar}$), 126.19 (*C*$_{Ar}$), 127.38 (*C*$_{Ar}$), 128.88 (*C*$_{Ar}$), 129.28 (*C*$_{Ar}$), 130.69 (*C*$_{Ar}$), 133.47 ($J^2_{C,F}$ = 32.25 Hz, *C*$_{Ar}$), 135.83 (*C*$_{Ar}$), 138.05 (*C*$_{Ar}$), 138.29 (*C*$_{Ar}$), 140.27 (*C*$_{Ar}$), 164.50 (C=O).

HRMS for **3a** (ESI) m/z calculated for $C_{17}H_{14}F_3NO$ (M+H)+: 306.11003, found: 306.11008.

6a. Yield: 86%, 0.24 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 1.66 (s, 3H, C*H*$_3$), 1.89 (s, 3H, C*H*$_3$), 2.33 (s, 3H, Ar-C*H*$_3$), 6.98–7.29 (m, 6H, Ar-*H*), 7.66 (s, 1H, N-*H*), 7.75–7.79 (m, 2H, Ar-*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm): δ 19.70 (*C*H$_3$), 20.17 (*C*H$_3$), 20.77 (*C*H$_3$), 115.26 (C=C), 115.55 (C=C), 125.58 (*C*$_{Ar}$), 127.42 (*C*$_{Ar}$), 127.71 (*C*$_{Ar}$), 129.47 (*C*$_{Ar}$), 129.57 (*C*$_{Ar}$), 129.68 (*C*$_{Ar}$), 130.09 (*C*$_{Ar}$), 130.20 (*C*$_{Ar}$), 130.98 ($J^2_{C,F}$ = 3.0 Hz, *C*$_{Ar}$), 163.50 ($J^1_{C,F}$ = 84.8 Hz, F-*C*$_{Ar}$), 166.27 (C=O).

HRMS for **6a** (ESI) m/z calculated for $C_{18}H_{18}FNO$ (M+H)+: 284.14452, found: 284.14448.

8f. E-isomer yield: 41%, 0.103 g. ^{1}H NMR (300MHz, $CDCl_3$ ppm): δ 1.48 (d, $J^3_{H,H}$ = 6.0 Hz, 3H, C*H*$_3$), 2.23 (s, 3H, Ar-C*H*$_3$), 6,72 (q, $J^3_{H,H}$ = 6.0 Hz, 1H, C=C*H*), 7.16–7.21 (m, 4H, Ar-*H*), 7.30 (m, 1H, Py-*H*), 7.76 (m, 1H, Py-*H*), 8.15 (m, 1H, Py-*H*), 8.36 (m, 1H, Py-*H*), 9.08 (s, 1H, N-*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm): δ 13.64 (*C*H$_3$), 19.27 (*C*H$_3$), 113.35 (C=C), 122.19 (C=C), 125.95 (*C*$_{Ar}$), 126.08 (*C*$_{Ar}$), 128.37 (*C*$_{Ar}$), 129.91 (*C*$_{Ar}$), 130.32 (*C*$_{Ar}$), 133.84 (*C*$_{Ar}$), 136.11 (*C*$_{Ar}$), 136.92 (*C*$_{Ar}$), 137.49 (*C*$_{Ar}$), 147.82 (*C*$_{Ar}$), 150.12 (*C*$_{Ar}$), 162.05 (C=O); **Z-isomer yield:** 37%, 0.093 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 1.77 (dd, $J^3_{H,H}$ = 6.0 Hz, $J_{H,N(H)}$ = 0.6 Hz, 3H, C*H*$_3$), 2.21 (s, 3H, Ar-C*H*$_3$), 5,37 (q, $J^3_{H,H}$ = 6.0 Hz, 1H, C=C*H*), 7.04–7.21 (m, 4H, Ar-*H*), 7.33 (m, 1H, Py-*H*), 7.74 (m, 1H, Py-*H*), 8.12 (m, 1H, Py-*H*), 8.45 (m, 1H, Py-*H*), 9.30 (s, 1H, N-*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm): δ 13.87 (*C*H$_3$), 20.13 (*C*H$_3$), 113.35 (C=C), 120.18 (C=C), 122.53 (*C*$_{Ar}$), 125.67 (*C*$_{Ar}$), 126.30 (*C*$_{Ar}$), 127.88 (*C*$_{Ar}$), 129.62 (*C*$_{Ar}$), 130.20 (*C*$_{Ar}$), 134.40 (*C*$_{Ar}$), 136.24 (*C*$_{Ar}$), 137.51 (*C*$_{Ar}$), 138.72 (*C*$_{Ar}$), 148.02 (*C*$_{Ar}$), 149.88 (*C*$_{Ar}$), 161.08 (C=O).

HRMS for **8f** (ESI) m/z calculated for $C_{16}H_{16}N_2O$ (M+H)+: 253.13354, found: 253.13364.

8g. E and Z isomers mixture. Total yield: 72%, 0.22 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 0.90 (d, $J^3_{H,H}$ = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$ for E isomer), 1.04 (d, $J^3_{H,H}$ = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$ for Z isomer), 1.98 (m, 1H, C*H*(CH$_3$)$_2$ for E isomer), 2.266 (s, 3H, Ar-C*H*$_3$, for E isomer), 2.271 (s, 3H, Ar-C*H*$_3$, for Z isomer), 2.60 (m, 1H, C*H*(CH$_3$)$_2$ for Z isomer), 3.75 (s, 3H, OC*H*$_3$, for E isomer), 3.77 (s, 3H, OC*H*$_3$, for Z isomer), 5.10 (d, $J^3_{H,H}$ = 10.5 Hz, 1H, C=C*H* for Z isomer), 6.42 (d, $J^3_{H,H}$ = 10.5 Hz, 1H, C=C*H* for E isomer), 6.77 – 7.72 (m, Ar-*H* and N-*H* for E and Z isomers); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm): δ 19.38 (*C*H$_3$ for E isomer), 20.22 (*C*H$_3$ for Z isomer), 22.62 (*C*H$_3$ for E isomer), 23.45 (*C*H$_3$ for Z isomer), 27.53 (*C*H for E isomer), 28.20 (*C*H for Z isomer), 55.41 (O*C*H$_3$), 113.82 (C=C for E isomer), 113.87 (C=C for Z isomer), 125.66 (*C*$_{Ar}$), 125.86 (*C*$_{Ar}$), 125.93 (*C*$_{Ar}$), 126.70 (*C*$_{Ar}$), 127.46 (*C*$_{Ar}$), 127.70 (*C*$_{Ar}$), 128.45 (*C*$_{Ar}$), 128.61 (*C*$_{Ar}$), 129.04 (*C*$_{Ar}$), 130.28 (*C*$_{Ar}$), 130.40 (*C*$_{Ar}$), 131.59 (*C*$_{Ar}$), 133.20 (*C*$_{Ar}$), 136.67 (*C*$_{Ar}$), 136.77 (*C*$_{Ar}$), 162.20 (C=O for Z isomer), 165.03 (C=O for E isomer).

HRMS for **8g** (ESI) m/z calculated for $C_{20}H_{23}NO_2$ (M+H)+: 310.18016, found: 310.17998.

11. Yield: 87%, 0.25 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.54 (d, 1H, $J^3_{H,H}$ = 3.0 Hz, Ar-*H*), 7.08 (d, 1H, $J^3_{H,H}$ = 3.0 Hz, Ar-*H*), 7.22–7.34 (m, 2H, Ar-*H*), 7.52 (d, $J^2_{H,H}$ = 9.0 Hz, 1H, Ar-*H*),), 7.68–7.76 (m, 4H, Ar-*H*), 8.32 (d, $J^2_{H,H}$ = 9.0 Hz, 1H, Ar-*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm): δ 109.48 (*C*$_{Ar}$), 116.47 (*C*$_{Ar}$), 119.92 ($J^1_{C,F}$ = 270.8 Hz, -*C*F$_3$), 121.08 (*C*$_{Ar}$), 124.39 (*C*$_{Ar}$), 125.31 (*C*$_{Ar}$), 125.70 (m, *C*$_{Ar}$), 126.97 (*C*$_{Ar}$), 129.38 (*C*$_{Ar}$), 130.79 (*C*$_{Ar}$), 133.48 ($J^2_{C,F}$ = 33.0 Hz, *C*$_{Ar}$), 135.93 (*C*$_{Ar}$), 137.97 (*C*$_{Ar}$), 167.27 (C=O).

HRMS for **11** (ESI) m/z calculated for $C_{16}H_{10}F_3NO$ (M+H)+: 290.07873, found: 290.07859.

General procedure for synthesis of N-acyl imines

To a vial (12 mL reaction volume) which was charged with $Pd(AcO)_2$ (1.2 mg, 0.005 mmol) and equipped with a septum, a small cannula and a stirring bar, **L1** (5.2 mg, 0.015 mmol), toluene (1.5 mL), TMEDA (0.11 mL), imine (1 mmol) were added. After addition of corresponding aryl bromide (1.2 mmol), the vials were placed in an alloy plate which was transferred to a 300 mL autoclave (4560 series from Parr Instruments®) under an argon atmosphere. The autoclave was flushed three times with CO and then pressurized to 5 bar CO and 17 bar N_2. The reaction was kept stirring at 115 °C for 18 h. After cooling down to room temperature, CO was released carefully. Pure product could be obtained by column chromatography on silica gel (general eluent: hexane/ethylacetate = 9:1).

Spectra data for selected N-acyl imines

13a. Yield: 90%, 0.30 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 2.20 (s, 3H, Ar-C*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 6.92 (d, 2H, $J^3_{H,H}$ = 9.0 Hz, Ar-*H*), 7.08–7.31 (m, 4H, Ar-*H*), 7.45–7.56 (m, 3H, Ar-*H*), 7.82 (m, 2H, Ar-*H*), 7.92 (d, 2H, $J^3_{H,H}$ = 9.0 Hz, Ar-*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, ppm): δ 20.20 (*C*H$_3$), 55.45 (O*C*H$_3$), 113.64 (*C*$_{Ar}$), 125.43 (*C*$_{Ar}$), 126.39 (*C*$_{Ar}$), 127.21 (*C*$_{Ar}$), 128.68 (*C*$_{Ar}$), 129.01 (*C*$_{Ar}$), 129.14 (*C*$_{Ar}$), 130.23 (*C*$_{Ar}$), 131.38 (*C*$_{Ar}$), 131.99 (*C*$_{Ar}$), 135.34 (*C*$_{Ar}$), 135.84 (*C*$_{Ar}$), 136.85 (*C*$_{Ar}$), 163.38 (*C*$_{Ar}$), 168.49 (C=N), 179.56 (C=O).

HRMS for **13a** (ESI) m/z calculated for $C_{22}H_{19}NO_2$ (M+H)+: 330.14886, found: 330.14895.

13i. Yield: 87%, 0.37 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 7.20 (m, 1H Ar-*H*), 7.25 (m, 1H, Ar-*H*), 7.36 (m, 1H, Ar-*H*), 7.60 (m, 2H, Ar-*H*), 7.94 (d, $J^2_{H,H}$ = 9.0 Hz, 1H, Ar-*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, ppm): δ 123.30 ($J^1_{C,F}$ = 226.5 Hz, -*C*F$_3$), 125.44 ($J^3_{C,F}$ = 3.8 Hz, *C*$_{Ar}$), 126.82 (*C*$_{Ar}$), 129.12 (*C*$_{Ar}$), 129.70 (*C*$_{Ar}$), 129.90 (*C*$_{Ar}$), 130.40 (*C*$_{Ar}$), 130.95 (*C*$_{Ar}$), 131.04 (*C*$_{Ar}$), 133.98 (*C*$_{Ar}$), 134.27 (*C*$_{Ar}$), 134.48 ($J^2_{C,F}$ = 32.8 Hz, *C*$_{Ar}$), 135.81 (*C*$_{Ar}$), 139.04 (*C*$_{Ar}$), 165.70 (*C*$_{Ar}$), 168.49 (C=N), 177.93 (C=O).

HRMS for **13i** (ESI) m/z calculated for $C_{21}H_{12}Cl_2F_3NO$ (M+H)+: 422.03208, found: 422.03217.

Synthesis of sterically hindered amides from N-acyl imines

To a 100 mL Schlenk tube which was charged with 30 mL THF solution of N-acyl imine (1 mmol) and equipped with a septum and a stirring bar, 15 mL THF solution of Grignard reagent (0.1 M) was added dropwise at 0 °C. After that, the mixture was allowed to be warmed to room temperature and kept stirring for 2 h. The reaction process was monitored by TLC. When N-imine was converted completely, 30 mL NH_4Cl saturated aqueous solution was added into the Schleck tube to quench the reaction. The product was extracted by ethyl ether (3 × 10 mL). Then this organic solution was dried by Na_2SO_4. After removal of organic solvent, pure product could be obtained by column chromatography on silica gel (general eluent: hexane/ethylacetate = 6:1).

Spectra data for sterically hindered amides

14a. Yield: 90%, 0.32 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 0.72 (t, $J^3_{H,H}$ = 7.2 Hz, 3H, C*H*$_3$), 1.81 (s, 3H, Ar-C*H*$_3$), 2.31 (m, 1H, C*H*$_2$), 3.18 (m, 1H, C*H*$_2$), 3.74 (s, 3H, OC*H*$_3$), 6.84 (d, $J^3_{H,H}$ = 8.7 Hz, 2H, Ar-*H*), 6.87 (s, 1H, C(O)N*H*), 6.95 (d, $J^3_{H,H}$ = 7.2 Hz, 1H, Ar-*H*), 7.08 – 7.13 (m, 3H, Ar-*H*), 7.16 – 7.26 (m, 4H, Ar-*H*), 7.69 (d, $J^3_{H,H}$ = 9.0 Hz, 2H, Ar-*H*), 7.75 (m, 1H, Ar-*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, ppm): δ 8.66 (*C*H$_3$), 22.08 (*C*H$_2$), 31.54 (Ar-*C*H$_3$), 55.45 (O*C*H$_3$), 65.15 (*C*-N), 113.88 (*C*$_{Ar}$), 125.50 (*C*$_{Ar}$), 125.66 (*C*$_{Ar}$), 126.83 (*C*$_{Ar}$), 127.30 (*C*$_{Ar}$), 127.44 (*C*$_{Ar}$), 127.71 (*C*$_{Ar}$), 128.35 (*C*$_{Ar}$), 128.61 (*C*$_{Ar}$), 132.76 (*C*$_{Ar}$), 135.98 (*C*$_{Ar}$), 143.12 (*C*$_{Ar}$),), 144.82 (*C*$_{Ar}$), 162.17 (*C*$_{Ar}$), 165.06 (C=O).

HRMS for **14a** (ESI) m/z calculated for $C_{24}H_{25}NO_2$ (M+H)+: 360.19581, found: 360.19558

14b. Yield: 84%, 0.36 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 0 (t, $J^3_{H,H}$ = 3.0 Hz, 3H, C*H*$_3$), 0.64 (m, 2H, C*H*$_2$), 1.30 (m, 2H, C*H*$_2$), 1.95 (s, 3H, Ar-C*H*$_3$), 2.54 (td, $J^2_{H,H}$ = 4.5 Hz, $J^3_{H,H}$ = 12.3 Hz, 1H, C*H*$_2$), 3.26 (td, $J^2_{H,H}$ = 4.5 Hz, $J^3_{H,H}$ = 12.3 Hz, 1H, C*H*$_2$), 3.82 (m, 1H, Si-*H*), 3.87 (s, 3H, OC*H*$_3$), 6.98 (d, $J^3_{H,H}$ = 9.0 Hz, 2H, Ar-*H*), 7.02 (s, 1H, C(O)N*H*), 7.22 – 7.39 (m, 7H, Ar-*H*), 7.81 – 7.89 (m, 3H, Ar-*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, ppm): δ -4.46 ($J^1_{Si,C}$ = 3.8 Hz, Si-*C*H$_3$), 14.18 (*C*H$_2$), 19.03 (*C*H$_2$), 22.04 (*C*H$_2$), 42.24 (Ar-*C*H$_3$), 55.41 (O*C*H$_3$), 64.92 (*C*-N), 113.86 (*C*$_{Ar}$), 125.47 (*C*$_{Ar}$), 125.59 (*C*$_{Ar}$), 126.81 (*C*$_{Ar}$), 127.27 (*C*$_{Ar}$), 127.54 (*C*$_{Ar}$), 127.70 (*C*$_{Ar}$), 128.34 (*C*$_{Ar}$), 128.57 (*C*$_{Ar}$), 132.76 (*C*$_{Ar}$), 135.92 (*C*$_{Ar}$), 143.04 (*C*$_{Ar}$),), 145.09 (*C*$_{Ar}$), 162.12 (*C*$_{Ar}$), 165.06 (C=O).

HRMS for **14b** (ESI) m/z calculated for $C_{27}H_{33}NO_2Si$ (M+H)+: 432.23533, found: 432.23531.

General procedure for synthesis of N-acyl imidates

To a vial (12 mL reaction volume) which was charged with $Pd(AcO)_2$ (2.2 mg, 0.01 mmol) and equipped with a septum, a small cannula and a stirring bar, **L1** (10.5 mg, 0.03 mmol), toluene (1.5 mL), Et_3N (0.21 mL), imidate (1 mmol) were added. After addition of corresponding aryl bromide (1.2 mmol), the vials were placed in an alloy plate which was transferred to a 300 mL autoclave (4560 series from Parr Instruments®) under an argon atmosphere. The autoclave was flushed three times with CO and then pressurized to 5 bar CO and 17 bar N_2. The reaction was kept stirring at 115 °C for 18 h. After cooling down to room temperature, CO was released carefully. Pure product could be obtained by column chromatography on silica gel (general eluent: hexane/ethylacetate = 6:1).

Spectra data for selected N-acyl imidates

16a. Yield: 83%, 0.26 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 4.05 (s, 3H, OC*H*$_3$), 7.21 (ddd, $J^3_{H,H}$ = 7.5 Hz, $J^4_{H,H}$ = 4.5 Hz, $J^5_{H,H}$ = 1.2 Hz, 1H, Ar-*H*), 7.60 (d, $J^3_{H,H}$ = 7.5 Hz, 2H, Ar-*H*), 7.70 (td, $J^3_{H,H}$ = 7.5 Hz, $J^5_{H,H}$ = 1.2 Hz, 1H, Ar-*H*), 7.84 (dt, $J^3_{H,H}$ = 7.5 Hz, $J^5_{H,H}$ = 1.2 Hz, 1H, Ar-*H*), 8.00 (d, $J^2_{H,H}$ = 7.5 Hz, 2H, Ar-*H*), 8.30 (m, 1H, Ar-*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, ppm): δ 55.35 (O*C*H$_3$), 123.68 (*C*$_{Ar}$), 123.86 ($J^1_{C,F}$ = 270.8 Hz, -*C*F$_3$), 125.18 (m, *C*$_{Ar}$), 125.85 (*C*$_{Ar}$), 129.13 (*C*$_{Ar}$), 133.18 ($J^2_{C,F}$ = 32.2 Hz, *C*$_{Ar}$), 137.22 (*C*$_{Ar}$), 138.61 (*C*$_{Ar}$), 145.37 (*C*$_{Ar}$), 148.71 (*C*$_{Ar}$), 155.68 (C=N), 176.20 (C=O).

HRMS for **16a** (ESI) m/z calculated for $C_{15}H_{11}F_3N_2O_2$ (M+H)+: 309.08454, found: 309.08457.

Synthesis of diacid anilides (19) from N-acyl imidate (16a)

To a 100 mL Schlenk tube which was charged with 30 mL THF solution of **16a** (1 mmol) and equipped with a septum and a stirring bar, 15 mL 0.1 M HCl was added dropwise at room temperature. After that, the mixture was heated to 50 °C and kept stirring at the same temperature for 2 h. The reaction process was monitored by TLC. When **16a** was converted completely, the product was extracted by ethyl ether (3 × 10 mL). Then this organic solution was dried by Na_2SO_4. After removal of organic solvent, pure product **19** was obtained by column chromatography on silica gel (general eluent: hexane/ethylacetate = 3:1).

Yield: 78%, 0.23 g. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 4.05 (s, 3H, OC*H*$_3$), 7.21 (ddd, $J^3_{H,H}$ = 7.5 Hz, $J^4_{H,H}$ = 4.5 Hz, $J^5_{H,H}$ = 1.2 Hz, 1H, Ar-*H*), 7.60 (d, $J^3_{H,H}$ = 7.5 Hz, 2H, Ar-*H*), 7.70 (td, $J^3_{H,H}$ = 7.5 Hz, $J^5_{H,H}$ = 1.2 Hz, 1H, Ar-*H*), 7.84 (dt, $J^3_{H,H}$ = 7.5 Hz, $J^5_{H,H}$ = 1.2 Hz, 1H, Ar-*H*), 8.00 (d, $J^2_{H,H}$ = 7.5 Hz, 2H, Ar-*H*), 8.30 (m, 1H, Ar-*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, ppm): δ 123.46 ($J^1_{C,F}$ = 270.8 Hz, -*C*F$_3$), 125.96 (m, *C*$_{Ar}$), 127.98 (*C*$_{Ar}$), 128.33 (*C*$_{Ar}$), 134.46 ($J^2_{C,F}$ = 33.0 Hz, *C*$_{Ar}$), 136.69 (*C*$_{Ar}$), 138.19 (*C*$_{Ar}$), 148.14 (*C*$_{Ar}$), 148.36 (*C*$_{Ar}$), 161.88 (C=8), 164.00 (C=O).
HRMS for **19** (ESI) m/z calculated for $C_{14}H_9F_3N_2O_2$ (M+H)+: 295.06889, found: 295.06894.

Synthesis of Pd(L1)(NMM) (22)

To a 100 mL Schlenk tube which was charged with 10 mL heptane solution of Pd(allyl)(Cp) (**20**) (0.816 mmol) and NMM (**21**) (0.816 mmol) and equipped with a septum and a stirring bar, 5 mL heptane solution of **L1** (0.866 mmol) was added dropwise at room temperature. After that, the mixture was kept stirring at the same temperature overnight. When the reaction finished, the solution was filtered and residue was re-dissolved by heptane/toluene at 50 °C. The solution was filtered again through Celite. The pale yellow crystal of **22** was obtained from this clear solution at 8 °C. Yield: 56%. ^{1}H NMR (400MHz, C_6D_6, ppm): δ 1.15 (d, $J^3_{H,P}$ = 16 Hz, 18H, C(C*H*$_3$)$_3$), 1.21 (d, $J^3_{H,P}$ = 16 Hz, 18H, C(C*H*$_3$)$_3$), 2.86 (s, 3H, N-C*H*$_3$), 3.53 - 3.74 (m, 4H, -OC*H*$_2$C*H*$_2$O-), 4.08 (d, $J^3_{H,H}$ = 4 Hz, 2H, C*H*=C*H*); ^{31}P{^{1}H} NMR (162 MHz, C_6D_6, ppm): δ 186.42 (s). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 22.98 (N-*C*H$_3$), 28.44 (d, $J^2_{C,P}$ = 49 Hz, C(*C*H$_3$)$_3$), 39.95 (d, $J^1_{C,P}$ = 118 Hz, *C*(CH$_3$)$_3$), 50.76 (d, $J^2_{C,P}$ = 27 Hz, *C*H=*C*H), 69.29 (OCH$_2$CH$_2$O), 175.96 (C=O).

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[18] CCDC 1560675 (compound **13b**) and 1560674 (compound **19**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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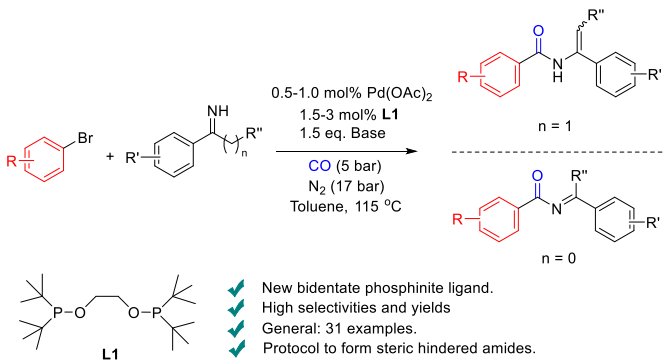

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An Efficient Protocol to Synthesize N-Acyl-Enamides and -Imines via Pd-catalyzed Carbonylations

The new phosphinite ligand 1,2-bis(di-*iso*-butylphosphinoxy)ethane (^{t}Bu$_2$POCH$_2$-CH$_2$OP^{t}Bu$_2$) allows for Pd-catalyzed carbonylation reaction of N-H imines to afford selectively N-acyl-enamides and -imines.