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## C–H Functionalization

# Pd-Catalyzed C(sp$^2$)–H Alkoxycarbonylation of Phenethyl- and Benzylamines with Chloroformates as CO Surrogates

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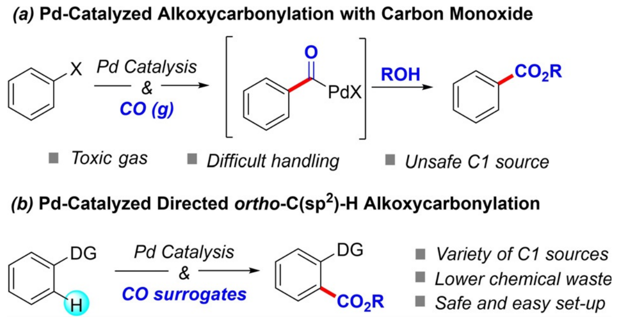
**Abstract:** The site-selective functionalization of C–H bonds within a complex molecule remains a challenging task of capital synthetic importance. Herein, an unprecedented Pd-catalyzed C(sp$^2$)–H alkoxycarbonylation of phenylalanine derivatives and other amines featuring picolinamide as the directing group (DG) is reported. This oxidative coupling is distinguished by its scalability, operational simplicity, and avoids the use of toxic carbon monoxide as the $C_1$ source. Remarkably, the easy cleavage of the DG enables the efficient assembly of isoindolinone compounds. Density Functional Theory calculations support a Pd$^{II}$/Pd$^{IV}$ catalytic cycle.

## Introduction

Carbonylation reactions are of paramount importance in both academic and industrial environments and represent a crucial technology for the production of bulk and fine chemicals worldwide.[1] One of the most relevant carbonylation processes is the palladium-catalyzed alkoxycarbonylation of aryl halides featuring the combination of CO (gas) as the $C_1$ source along with an alcohol for the introduction of the ester unit (Scheme 1, *route a*).[1] Despite its high abundance and low price, the use of carbon monoxide poses severe downsides such as high risk in handling and storage as well as toxicity and flammability, among others. As a result, a myriad of CO surrogates have been investigated in the last several years to perform carbonylation reactions in a safer and sustainable fashion.

Compared with classical syntheses occurring in pre-functionalized substrates, C–H functionalization has changed the landscape of modern chemistry by enabling the direct conversion of traditionally unreactive hydrocarbon moieties into valuable functionalized compounds.[2] In particular, the chelation assistance approach based on the installation of a Lewis basic motif commonly named directing group (DG) offers a more streamlined and atom-efficient approach to chemical synthesis.[3] This tactic has allowed for the challenging site-selective appendance of a variety of CO surrogates at the *ortho* position of non-functionalized arenes such as carbon dioxide,[4] α-keto esters,[5] azodicarboxylates,[6] DMF,[7] chloroform,[8] or alkyl chloroformates,[9] among others (Scheme 1, *route b*). Although the latter methods have clearly expanded the toolkit of available carbonylations, the selective C–H alkoxycarbonylation[10] occurring at C sites remotely positioned from a given DG still remains an unmet challenge of prime synthetic significance.




**Scheme 1.** Pd-catalyzed alkoxycarbonylations.

The recent years have witnessed a tremendous interest in the chemical modification of amino acids and peptides derived thereof.[11] In this regard, transition-metal catalysis has unlocked new paradigms for the site-selective labeling of a vast array of amino acids and fueled the development of innovative bond disconnections upon C–H functionalization processes.[12] In 2016, the group of Shi designed an efficient Pd-catalyzed C(sp$^3$)–H alkoxycarbonylation with alkyl chloroformates as the practical $C_1$ source for the modification of a broad range of aliphatic carboxamides bearing 8-aminoquinoline (AQ) as the DG.[13a] Remarkably, a wide variety of phenylalanine (Phe) residues housing the DG at the C-terminal position smoothly underwent the selective alkoxycarbonylation at the benzylic site through the formation of a five-membered palladacycle

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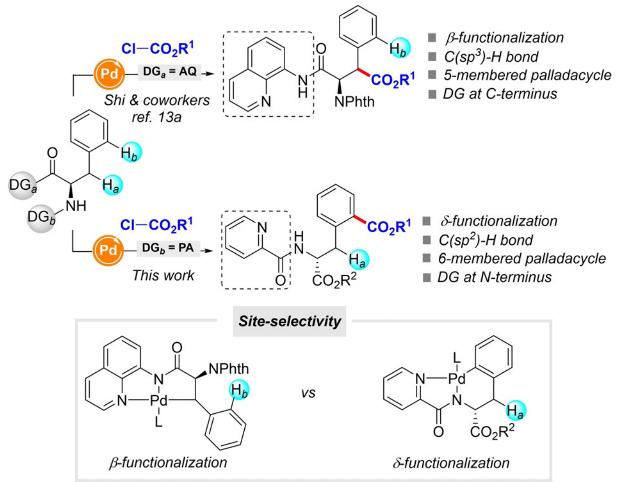



**Scheme 2.** Alkoxycarbonylation of Phe derivatives.

(Scheme 2, top). More recently, they have achieved the assembly of a number of phthalic acid derivatives through a Pd-catalyzed AQ-directed C($sp^2$)–H alkoxycarbonylation process.[13b]

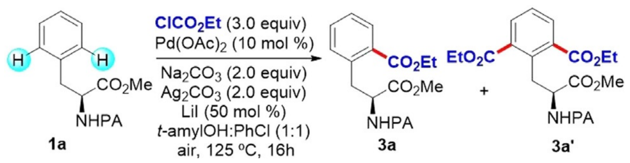
Inspired by these excellent results, we envisioned a complementary amino acid tagging technique featuring the installation of picolinamide (PA) as bidentate auxiliary at the N-terminus of the Phe residue, thus enabling the remote δ-functionalization upon the intermediacy of a challenging six-membered palladacycle (Scheme 2, bottom). Assuming an analogous mechanism to that proposed by Shi involving a $Pd^{II}/Pd^{IV}$ regime,[13] we anticipated that the judicious choice of the reaction parameters would be crucial for achieving high positional selectivity. In fact, careful analysis of the existing literature clearly verified that site-selectivity issues may hamper the targeted δ-functionalization as the transient $Pd^{IV}$ intermediate could undergo competitive reductive elimination processes to deliver either the N-functionalized product or the corresponding indoline compound upon an intramolecular C–H amination reaction.[14] To the best of our knowledge, the C($sp^2$)–H alkoxycarbonylation of β-arylethylamines remains unexplored and, if successful, we could unlock its full synthetic potential toward the diversification of other arylamines beyond phenylalanine derivatives. As part of our interest in C–H functionalization,[15] herein we disclose a Pd-catalyzed site-selective C($sp^2$)–H alkoxycarbonylation of picolinamide-containing phenethyl and benzyl amines with chloroformates. The salient features of our method include the broad group tolerance, scalability, retention of the native chirality, and facile removal of the required DG, thus streamlining the assembly of biologically relevant isoindolinone framework in the absence of carbon monoxide. Likewise, Density Functional Theory (DFT) studies unraveled a $Pd^{II}/Pd^{IV}$ catalytic manifold and rationalized the common use of *tert*-amyl alcohol as a non-innocent solvent in C–H functionalization reactions.

## Results and Discussion

Since the seminal work by Daugulis on the use of picolinamide (PA) as a removable, efficient DG,[16] it has demonstrated superior directing abilities to assist a variety of transformations in the realm of C–H activation.[17] Encouraged by these results, we began our studies by selecting the alkoxycarbonylation of PA-Phe-OMe (**1a**) with commercially available ethyl chloroformate (**2a**) as the model reaction. Whereas the formation of the indoline derivative through an intramolecular δ-amination was never detected,[14] initial exploratory screening preferentially afforded the undesired N-functionalized product. Control experiments in the absence of $Pd(OAc)_2$ ruled out the formation of the latter compound through a classical base-assisted substitution reaction and supported a C–N bond-forming reductive elimination of the putative $Pd^{IV}$ species (see below). However, careful screening of all the reaction parameters revealed that the latter reaction pathway could be minimized and achieved the desired δ-alkoxycarbonylation instead.[18]

After considerable experimentation, we found that the combination of $Pd(OAc)_2$ (10 mol %), $Na_2CO_3$, $Ag_2CO_3$, LiI as additive in a mixture of *t*-amyl alcohol and PhCl at 125 °C under air provided the best results, giving rise to **3a** in 75 % yield as a mixture of mono- and di-alkoxycarbonylated products (1:3 ratio; Table 1, entry 1). Control experiments proved instructive in understanding the requirements of the process: whereas the Pd catalyst and silver carbonate had a crucial role as not even traces of **3a** were detected in their absence (entries 2 and 3, respectively), the addition of $Na_2CO_3$ and LiI was found to be beneficial and resulted in higher yields of **3a** (entries 4 and 5, respectively). Other iodide sources afforded **3a** in lower yields (entries 6 and 7). Likewise, the use of a mixture of PhCl and

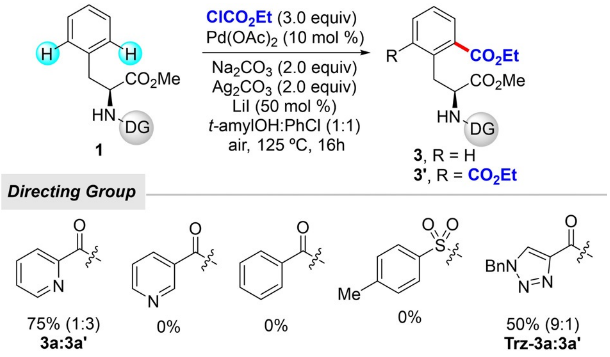
**Table 1.** Pd-catalyzed δ-C($sp^2$)–H alkoxycarbonylation of PA-Phe-OMe with ethyl chloroformate.[a]




| Entry | Change from standard conditions | **3a** [%][b] |
|---|---|---|
| 1 | none | 75 (1:3)[c] |
| 2 | without $Pd(OAc)_2$ | 0 |
| 3 | without $Ag_2CO_3$ | 0 |
| 4 | without $Na_2CO_3$ | 42 (3:1)[c] |
| 5 | without LiI | 30 (1:3)[c] |
| 6 | TBAI instead of LiI | 0 |
| 7 | KI instead of LiI | 51 (1:3)[c] |
| 8 | $Na_2CO_3$ (1.0 equiv) | 64 (1:3)[c] |
| 9 | $Ag_2CO_3$ (1.0 equiv) | 58 (1:3)[c] |
| 10 | PhCl as solvent | 54 (3:1)[c] |
| 11 | *t*-amylOH as solvent | 46 (3:1)[c] |

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (10 mol %), $Ag_2CO_3$ (2.0 equiv), $Na_2CO_3$ (2.0 equiv), LiI (50 mol %) in a mixture of *t*-amylOH/PhCl (1:1; 2 mL) at 125 °C for 16 h under air. [b] Yield of isolated product after column chromatography. [c] Ratio of mono- and difunctionalized product **3a**/**3a'**.

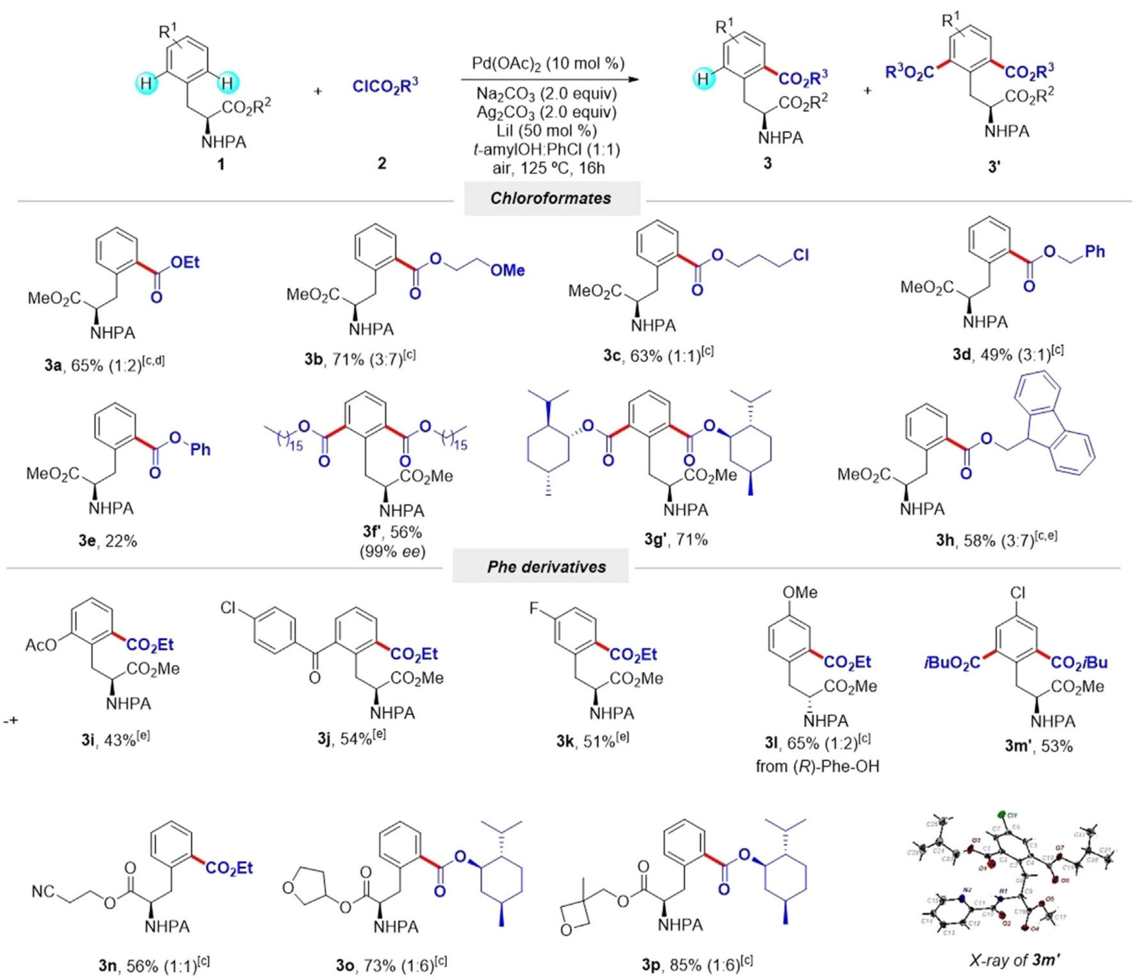
*tert*-amyl alcohol led to the best results (entries 10 and 11). To overcome the persistent problem of regioselectivity between the mono- and di-functionalization reaction, the evaluation of supporting ligands, equivalents of **2a** and other parameters were carefully analyzed. Unfortunately, higher selectivity toward the mono-alkoxycarbonylated product **3a** was only achieved at the expense of having much lower overall yields. Importantly, different DGs were evaluated under the optimized conditions and PA showed a superior coordinating ability as a bidentate DG (Scheme 3). In this regard, benzoyl- and tosyl-protected Phe derivatives devoid of an additional nitrogen-chelating atom remained unreactive as well as the parent derivative bearing a 3-pyridine unit, thereby supporting the bidentate nature of PA. Likewise, a related carboxamide housing a 1,2,3-triazole unit could be also employed as an efficient bidentate DG, albeit with lower efficiency.




**Scheme 3.** Influence of the DG.

We next investigated the preparative scope of the δ-C($sp^2$)–H alkoxycarbonylation protocol to assemble a new family of decorated Phe compounds in a simple fashion (Table 2). Gratifyingly, the model substrate PA-Phe-OMe (**1a**) smoothly underwent the target alkoxycarbonylation with a wide variety of electronically diverse chloroformates. Not only simple alkyl chloroformates such as ethyl (**2a**), benzyl (**2d**), hexadecyl (**2f**), and 9-fluorenylmethyl (**2h**) derivatives but also structurally complex menthyl chloroformate (**2g**) furnished the corresponding products **3** as variable mixtures of mono- and di-al-

**Table 2.** Pd-catalyzed δ-C($sp^2$)–H alkoxycarbonylation of phenylalanine derivatives.[a,b]




[a] As for Table 1, entry 1. [b] Yield of isolated product or product mixture after column chromatography, average of at least two independent runs. [c] Ratio of mono- and diacylated product (**3**/**3'**). [d] Gram-scale experiment. [e] *t*-amylOH/PhCl (1:1; 4 mL).

koxycarbonylated compounds, which were separated by column chromatography. Notably, the process was tolerant of chloroformates bearing methoxy and chloro groups within the alkyl chain, thereby affording the corresponding Phe compounds **3b** and **3c**, respectively, in high yields. Whereas benzyl chloroformate preferentially delivered the mono-carbonylated product **3d** in 49% yield, hexadecyl and 9-fluorenylmethyl derivatives resulted in the exclusive formation of difunctionalized Phe compounds **3f′** and **3g′** in 56 and 71% yield, respectively. Importantly, aryl chloroformates such as **2e** could be also used, albeit with lower efficiency. The use of unnatural Phe derivatives accommodating different substitution patterns within the aromatic ring led to the exclusive formation of the mono-alkoxycarbonylated compounds. In this regard, Phe residues bearing *ortho* or *meta* substituents, which blocked the difunctionalization process, resulted in **3i–k** in good yields. Conversely, *para*-substituted Phe residues resulted in the preferential (**3l**) or exclusive formation (**3m′**) of the difunctionalized product. Importantly, HPLC analysis of **3f′** verified that no racemization occurred along the oxidative process,[18] and crystallographic analysis of **3m′** confirmed that the absolute stereochemistry was identical to that of the starting Phe residue. Notably, the method boded well with Phe derivatives bearing alkylnitriles (**3n**) as well as biologically relevant cyclic ethers (**3o** and **3p**). Furthermore, the process could be performed on the gram-scale with a remarkable 65% yield, thus highlighting the synthetic utility and robustness of our δ-C($sp^2$)–H alkoxycarbonylation manifold.

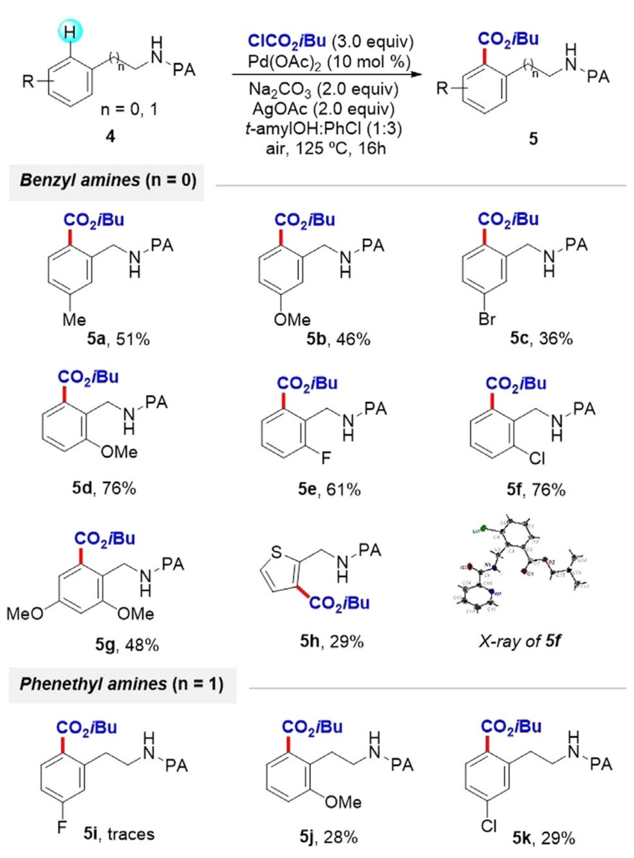
Deposition Numbers 2063453 (**3m′**), 2063455 (**5f**), and 2063452 (**6b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Although the method described by Shi was not applied to a more challenging peptide framework,[13a] we submitted a variety of picolinamide-protected Phe dipeptides to the developed reaction conditions. However, PA-Phe-Gly-OMe, PA-Phe-Phe-OMe, and PA-Phe-Pro-OMe remained unreactive.[18] In stark contrast, a wide variety of simple benzyl amines bearing the PA as DG smoothly underwent the mono-functionalization process to furnish compounds **5a–h** in moderate to good yields after slight modification of the reaction conditions (Table 3). The latter would occur through the formation of a kinetically more favored five-membered palladacycle. This protocol complements the method by Shi for the assembly of phthalic acid derivatives from benzamides bearing AQ as the DG,[13b] thereby enabling the γ-C($sp^2$)–H alkoxycarbonylation of simple benzyl amines.

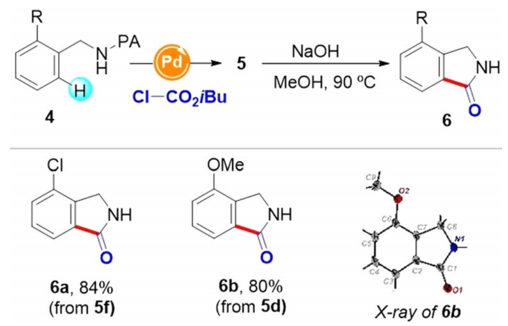
To our surprise, other simple β-arylethylamines devoid of the ester group of the corresponding Phe residue resulted in the corresponding alkoxycarbonylated products **5i–k** in low yields (Table 3). We hypothesized that the ester motif of the Phe unit could have a key role in the stabilization of the transient intermediates and a Thorp–Ingold effect could not be discarded.

Notably, the removal of the DG could be easily performed upon treatment with NaOH[19] with simultaneous hydrolysis of the ester motif, thus delivering the corresponding benzolactam compounds through an intramolecular condensation event in excellent yields (Scheme 4). X-Ray analysis of compound **6b** verified the formation of the N-unprotected heterocyclic core. This tandem alkoxycarbonylation/deprotection sequence offers an attractive alternative to the commonly used Pd-catalyzed carbonylation techniques of alkylamines, which customarily involve the use of toxic and flammable CO (gas).[20]

**Table 3.** Pd-catalyzed C($sp^2$)–H alkoxycarbonylation of benzylamines and phenethylamines.[a,b]




[a] Reaction conditions: **4** (0.25 mmol), $ClCO_2iBu$ (0.75 mmol), $Pd(OAc)_2$ (10 mol%), $Na_2CO_3$ (2.0 equiv), AgOAc (2.0 equiv) in a mixture of *t*-amylOH/PhCl (1:3; 4 mL) at 125 °C for 16 h under air. [b] Yield of isolated product after column chromatography, average of at least two independent runs.

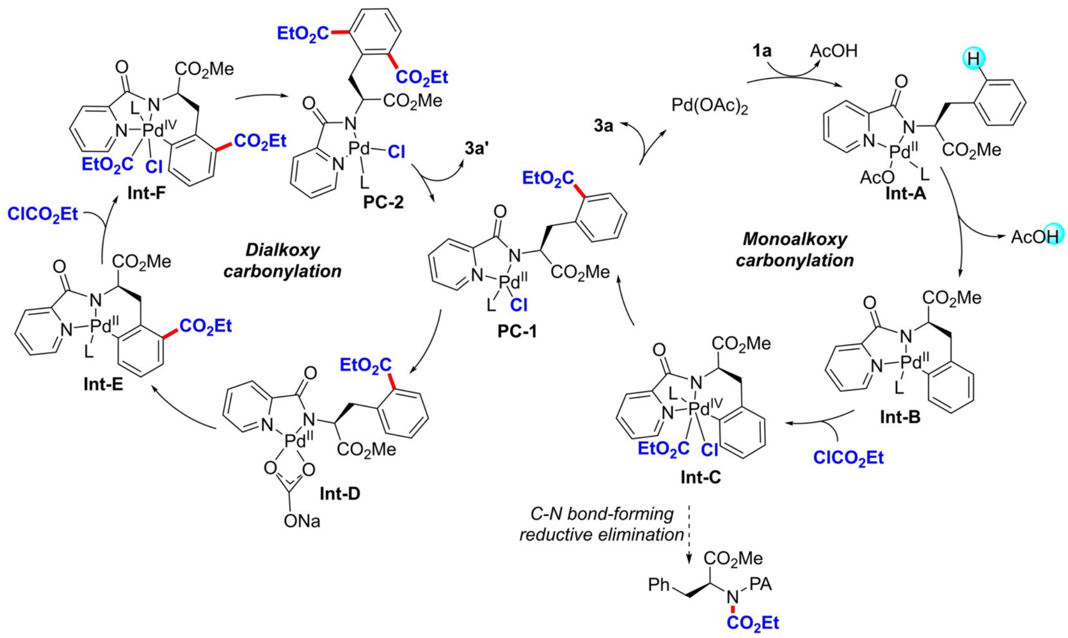



**Scheme 4.** Assembly of isoindolinones upon cleavage of the DG.

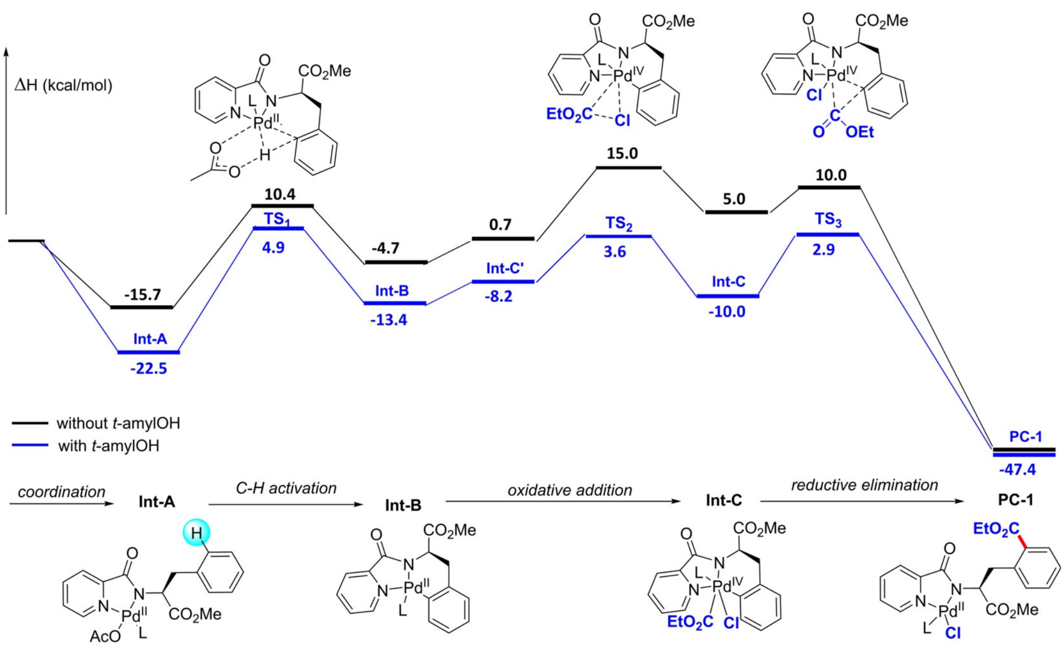
To understand the reaction pathway as well as some of the observed experimental evidences, we further performed DFT studies for the C(sp$^2$)–H alkoxycarbonylation of PA-Phe-OMe (**1 a**) with $ClCO_2Et$ (**2 a**). Assuming a similar reaction pathway to that of related PA-directed Pd-catalyzed C–H functionalization processes,[15d,17] we proposed the mechanism depicted in Scheme 5 entailing monomeric palladium intermediates. Complexation of **1 a** with $Pd(OAc)_2$ would initially afford Pd$^{II}$ complex **In-tA**,[15d,17c] which would next undergo a directed *ortho*-selective cyclometallation to provide the six-membered palladacycle **IntB**.[21] The latter would next undergo oxidative addition with ethyl chloroformate to provide the corresponding Pd$^{IV}$ **IntC**, which would ultimately deliver the mono-carbonylated product complex **PC-1** through a C–C bond-forming reductive elimination. Eventually, **PC-1** could either release product **3 a**, thereby recovering the active catalyst, or undergo a second functionalization event to yield di-alkoxycarbonylated derivative **3 a′**. Notice that in this study, to ensure the continuity of the reaction energy profiles, infinitely separated reactants and products are considered along with reactant complexes, transition states, intermediates, and products. Hence, with the aim of avoiding the unphysical overestimation of entropic effects owing to the lack of inclusion of explicit solvent molecules, all the energetic discussion will be carried out with enthalpies.[22]

Owing to the subtleties of our catalyst system including the use of *t*-amylOH as solvent as well as $Ag_2CO_3$ and LiI as additives, we anticipated that they could have a crucial role in favoring the formation of some of the putative reaction intermediates. We experimentally observed that the nature of the solvent had a profound effect on the reaction rate, yield, and selectivity of the process. Indeed, competitive *N*-alkoxycarbonylation (resulting from reductive elimination from **Int-C**) and hydrolysis of the ester group under basic conditions could be inhibited when adding *t*-amylOH to the reaction medium. Accordingly, DFT calculations were undertaken both in the absence and presence of *t*-amylOH molecules in an implicit manner (Scheme 6, black and blue reaction pathway, respectively).[18] With the energy values in hand, we can conclude that the reaction pathway when considering *t*-amylOH is energetically more favored and the latter showed a high stabilizing effect through coordination of the alcohol to the metal center and the formation of hydrogen bonds with the ester group of the Phe residue.

Although the whole reaction pathway is energetically more favored, the stabilization effect is stronger on the oxidative addition step. In fact, without considering the effect of *t*-amylOH, the oxidative addition step would be endothermic. In contrast, with the aid of the solvent molecules, this step would become exothermic. As a result, under these reaction conditions the C(sp$^2$)–H alkoxycarbonylation could be favored over other competitive side reactions, such as the *N*-alkoxycarbonylation reaction and the basic hydrolysis of the ester group. As mentioned above, the proposed mechanism would involve three fundamental steps. The first one would consist of the formation of **Int-A** through deprotonation and coordination of substrate **1 a** to the initial catalyst, leading to a reactant complex stabilized by $-22.5\ kcal\,mol^{-1}$ with respect to the separated species. The latter would next undergo a C–H activation event to afford **Int-B** through **TS$_1$**. Although this path could proceed through different mechanisms, we have assumed a CMD pathway wherein the C–H bond activation was assisted by an auxiliary carboxylate/carbonate ion acting as a base, which is often invoked in the directed *ortho*-palladation of aromatic substrates.[23] The optimized structure of the transition state (**TS$_1$**) reveals an elongation of the C–H bond from 1.08 to 1.38 Å and the approximation of the O atom to the H atom ($d_{O\text{-}H}$ = 1.34 Å) coupled with the formation of the Pd–C bond ($d_{Pd\text{-}C}$ =




**Scheme 5.** Proposed mechanism for the δ-alkoxycarbonylation of **1 a** with $ClCO_2Et$.



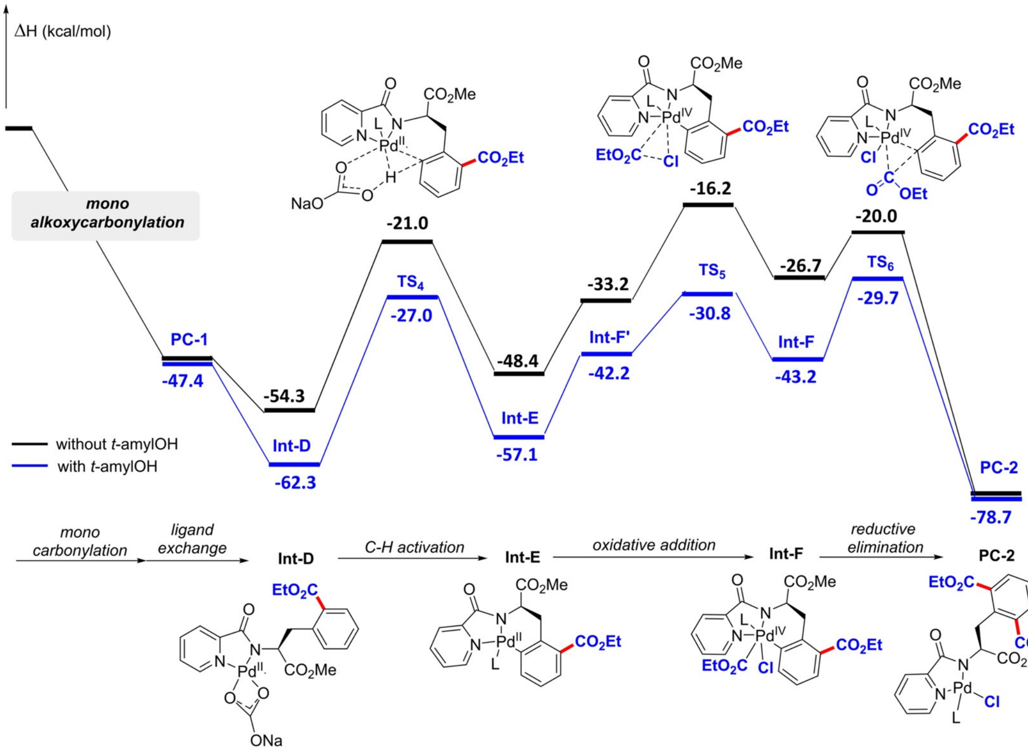

**Scheme 6.** Energy profile for the δ-(mono)alkoxycarbonylation of **1 a** with $ClCO_2Et$.

2.17 Å). In this case, the C–H activation step would be the rate-limiting step of the catalytic cycle with a barrier of 27.4 kcal mol$^{-1}$. Intermediate **Int-B** would next coordinate with ethyl chloroformate to deliver **Int-C**′ with an energy penalty of 5.2 kcal mol$^{-1}$. The optimized structure of this intermediate reveals a Pd–C bond length of 2.63 Å. The latter would undergo oxidative addition through a concerted pathway with a barrier of 11.8 kcal mol$^{-1}$ to afford thermodynamically favored $Pd^{IV}$ species **Int-C** through **TS$_2$**. In this three-membered transition state, the Pd–Cl and Pd–C distances are shortened to 2.42 and 2.23 Å, respectively, whereas the C–Cl distance is lengthened to 2.02 Å. With the formation of **Int-C** and dissociation of the C–Cl bond, the Pd–Cl and Pd–C distances are shortened and maintained over 1.96 and 2.36 Å, respectively. Although this species has been proposed to exist as both monomeric $Pd^{IV}$ and dimeric $Pd^{III}$ species, we have considered the monomeric form owing to its relative stability. Finally, this reactant complex could undergo a reductive elimination with a barrier of 12.9 kcal mol$^{-1}$ via a three-membered transition state **TS$_3$**, in which the C–C distance is shortened to 2.03 Å and the Pd–C distance is lengthened in 0.11 Å, leading to the thermodynamically favored product complex **PC-1** with an energy of −47.4 kcal mol$^{-1}$. At this point, two possible scenarios could occur: the dissociation of the product complex to provide the mono-functionalized product **3 a**, thereby releasing the active $Pd^{II}$ catalyst, or a series of ligand exchange reactions to deliver **Int-D**, which could undergo the second C–H functionalization process (Scheme 7). It is worth noting that the formation of **Int-D** has been simplified and reduced to a simple one-step reaction. In this regard, despite the fact that the presence of silver carbonate was found to be indispensable for the process to occur, its actual role cannot be attributed as a mere halide scavenger as heterodimeric Pd–Ag intermediates[24] could be also formed within our catalytic cycle.

The formation of the di-alkoxycarbonylated product **3 a**′ would take place following an analogous catalytic cycle featuring C–H functionalization, oxidative addition, and reductive elimination steps.[25] The geometries of the transient species are similar to those mentioned in the catalytic cycle toward the mono-alkoxycarbonylated compound **3 a**. As depicted in Scheme 7, the C–H activation event is also the rate-limiting step with an energy barrier of 35.3 kcal mol$^{-1}$. Moreover, not only the oxidative addition (**TS$_5$**) and reductive elimination (**TS$_6$**) steps, with energy barriers of 11.4 and 13.5 kcal mol$^{-1}$, respectively, but also all the intermediates described are energetically viable. Therefore, the thermodynamically favored product complex **PC-2** would be easily formed at the optimized reaction conditions involving a reaction temperature of 125 °C. As in the first catalytic cycle, coordination of the transient species with *t*-amylOH led to a more favored reaction pathway (blue vs. black pathway in Scheme 7).

Concerning the key role of LiI within the reaction outcome, we performed some DFT calculations assuming a ligand exchange prior to the reductive elimination step but we did not obtain any significant energy values.[18] Accordingly, further studies are required to clarify the role of iodide additives as they could accelerate other fundamental steps and, likewise, the intermediacy of iodide-bridged Pd dimers could not be discarded.[26]

Finally, we carried out some calculations to rationalize the experimentally observed lower or lack of reactivity of aryl chloroformates and dipeptides devoid of the ester motif within our alkoxycarbonylation manifold. As shown on Figure S3 (in the Supporting Information),[18] the kinetic barriers and the thermodynamic values when using $ClCO_2Ph$ are similar to those obtained with highly reactive $ClCO_2Et$; however, the use of $ClCO_2Ph$ led to the target product **3 e** in low yields (Table 2). Accordingly, we hypothesized that its lower reactivity might be




**Scheme 7.** Energy profile for the δ-(di)alkoxycarbonylation of **1 a** with $ClCO_2Et$.

derived from unproductive reaction pathways. Concerning the lack of reactivity of related Phe-containing dipeptides, computational studies with PA-Phe-Gly-OMe as the model substrate were undertaken. As depicted on Figures S4 and S5 (in the Supporting Information),[18] the nitrogen atom of the peptide backbone could also coordinate to the palladium center, thereby resulting in a distinct reaction intermediate that could eventually undergo oxidative addition of $ClCO_2Et$ instead of the desired C($sp^2$)–H carbonylation reaction. In agreement with the experiments, the use of dipeptides could result in an energetically more favored *N*-alkoxycarbonylation event.

## Conclusion

We have developed an unprecedented site-selective δ-C($sp^2$)–H alkoxycarbonylation technique for the modification of a variety of Phe residues in a simple fashion. This protocol avoids the use of toxic carbon monoxide as the $C_1$ source and complements the method by Shi for the installation of ester moieties now at remote sites of Phe derivatives. Notably, this alkoxycarbonylation reaction could be also applied in simple benzylamines and upon cleavage of the DG, it results in the assembly of the privileged isoindolinone core in a straightforward manner and in the absence of commonly used carbon monoxide. Salient features of the protocol are the scalability, the functional group tolerance, and the performance under air, which represents a practical bonus in terms of operational simplicity. Computational studies supported a $Pd^{II}/Pd^{IV}$ catalytic cycle and provided valuable insights into the reaction mechanism such as the key role of *t*-amylOH as co-solvent. We anticipate that this Pd-catalyzed oxidative C–H carboxylation manifold could become a useful synthetic tool for the rapid diversification of a virtually unlimited set of β-arylethylamines and benzylamines.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** alkoxycarbonylation · benzylamine · C–H functionalization · DFT calculations · phenylalanine

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