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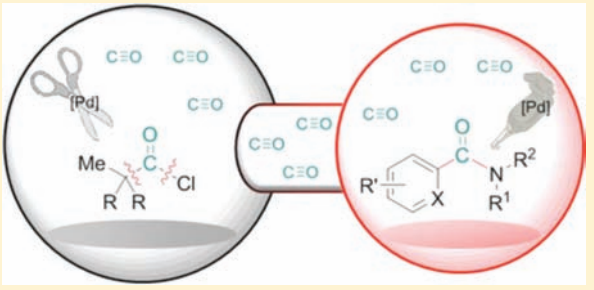
Ex Situ Generation of Stoichiometric and Substoichiometric ^{12}CO and ^{13}CO and Its Efficient Incorporation in Palladium Catalyzed Aminocarbonylations

Philippe Hermange, Anders T. Lindhardt,* Rolf H. Taaning, Klaus Bjerglund, Daniel Lupp, and Troels Skrydstrup*

The Center for Insoluble Protein Structures (inSPIN), Department of Chemistry and the Interdisciplinary Nanoscience Center, Aarhus University, Langelandsgade 140, 8000 Aarhus, Denmark

Supporting Information

ABSTRACT: A new technique for the *ex situ* generation of carbon monoxide (CO) and its efficient incorporation in palladium catalyzed carbonylation reactions was achieved using a simple sealed two-chamber system. The *ex situ* generation of CO was derived by a palladium catalyzed decarbonylation of tertiary acid chlorides using a catalyst originating from $Pd(dba)_2$ and $P(tBu)_3$. Preliminary studies using pivaloyl chloride as the CO-precursor provided an alternative approach for the aminocarbonylation of 2-pyridyl tosylate derivatives using only 1.5 equiv of CO. Further design of the acid chloride CO-precursor led to the development of a new solid, stable, and easy to handle source of CO for chemical transformations. The synthesis of this CO-precursor also provided an entry point for the late installment of an isotopically carbon-labeled acid chloride for the subsequent release of gaseous [^{13}C]CO. In combination with studies aimed toward application of CO as the limiting reagent, this method provided highly efficient palladium catalyzed aminocarbonylations with CO-incorporations up to 96%. The *ex situ* generated CO and the two-chamber system were tested in the synthesis of several compounds of pharmaceutical interest and all of them were labeled as their [^{13}C]carbonyl counterparts in good to excellent yields based on limiting CO. Finally, palladium catalyzed decarbonylation at room temperature also allowed for a successful double carbonylation. This new protocol provides a facile and clean source of gaseous CO, which is safely handled and stored. Furthermore, since the CO is generated *ex situ*, excellent functional group tolerance is secured in the carbonylation chamber. Finally, CO is only generated and released in minute amounts, hence, eliminating the need for specialized equipment such as CO-detectors and equipment for running high pressure reactions.



INTRODUCTION

Carbon monoxide (CO) has throughout the recent decades, in combination with transition metal catalysis, become a versatile reagent in organic synthesis.[1] Not only does the introduction of CO into a complex molecule add an extra carbon to the growing molecule, it simultaneously introduces a carbonyl group, one of the most common functionalities in bioactive compounds. These intrinsic qualities of CO in combination with recent developments in transition metal catalysis make this diatomic molecule an obvious reagent for the synthetic chemist. The bulk chemical industry also takes advantage of CO as a cost efficient C1 building block, transforming olefins into aldehydes, carboxylic acid derivatives, or alcohols by way of carbonylation reactions,[1i,2] thus, providing a straightforward access to valuable intermediates for the synthesis of polymers and other consumables.[3]

Since the first reports by Heck and co-workers in the 1970s on palladium catalyzed carbonylation reactions, the scope of CO chemistry has expanded considerably.[4] CO is a high affinity ligand for palladium, in oxidation states 0 and II, by its dual ability to act as a σ-donor and π-acceptor.[1b] The classical examples of Pd-catalyzed carbonylative couplings using halides or pseudohalides with a suitable nucleophile include alkoxycarbonylation,[1,5] aminocarbonylation,[1,6] carbonylative Heck,[1,7] carbonylative Suzuki–Miyaura,[1,8] carbonylative Sonogashira reactions,[1,9] and so forth. Whereas, alkoxycarbonylation using alcohols as the nucleophile is one of the most developed and robust method for the preparation of esters, the aminocarbonylation reaction creates an amide bond, which is of high interest to the pharmaceutical industry.[1c,10] Furthermore, transition metal catalyzed carbonylation reactions hold the advantage of introducing the carbonyl functionality in one step by electrophilic means. Traditionally, carbonyl functionalities are installed by trapping carbon dioxide with a suitable nucleophile, being typically organolithium, organozinc, or Grignard reagents, and subsequently transforming the formed acid into the desired product.[11] The latter method compromises the functional group tolerance of the system due to the presence of highly basic or nucleophilic reagents and requires

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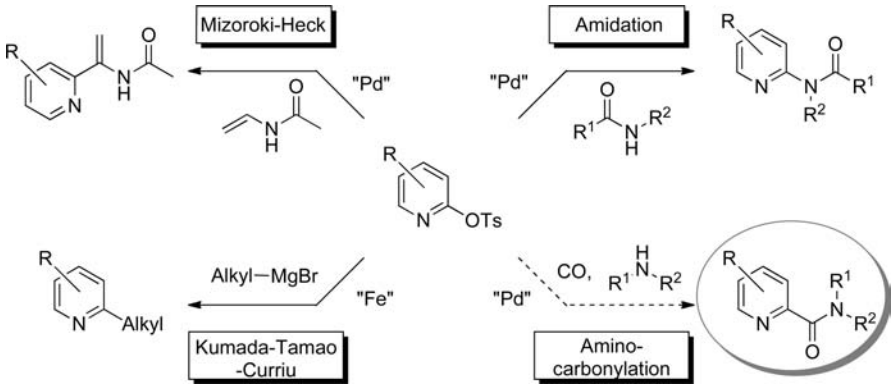


Figure 1. 2-Pyridyl toslylates in transition metal catalysis.

the carbonyl moiety to be installed early in the synthesis. By applying palladium catalysis, the acid derivative can be installed almost at any desired step in a synthesis due to the mild and selective conditions under which carbonylations are performed.

The majority of the published work on palladium-catalyzed carbonylations requires CO at elevated pressures whereby the use of 30−50 bar is not uncommon.[1] However, lately several important protocols developed by the groups of Beller, Buchwald and others have provided the possibility to perform palladium catalyzed carbonylations at near atmospheric pressure using only a syringe connected balloon as the CO-reservoir for the reaction or autoclaves pressurized in the range of 2−5 bar.[5d,h,6a,6e,6g,7a,7b,8m,9b,12]

Despite all the above-mentioned advantages of CO gas as a reagent in combination with transition metal catalysis, some lack of academic interest toward this field is still eminent. This reluctance is undoubtedly related to the properties of CO gas, being a highly toxic gas excluding oxygen from binding to hemoglobin leading to asphyxiation. Furthermore, CO is invisible, odorless and tasteless and side effects of CO only appear at late stage exposure. This in turn requires that CO is handled with extreme caution, including storage and transport, and its use is often accompanied with CO detectors and other specialized high-pressure equipment.

To overcome the dangers involved using CO gas, several groups have developed CO-equivalents. such as alkyl formates, formamides, formic anhydride, chloroform, aldehydes, an so forth.[1e,13,14] However, such equivalents generally require the presence of a transition metal catalyst and strong base in combination with high temperatures (>100 °C) to release CO. Although interesting, compatibility issues between the CO-producing and CO-consuming reaction severely limits the degree of overall molecular complexity. One special class of solid *in situ* CO-releasing molecules is the metal carbonyls, such as $Fe(CO)_5$, $Cr(CO)_6$, $W(CO)_6$, $Co_2(CO)_8$, and especially $Mo(CO)_6$, which have been extensively studied by the group of Larhed and others.[13b−f,14] Despite that $Mo(CO)_6$ currently represents the best alternative to CO-gas, it still adds near stoichiometric amounts of an additional transition metal, namely, Mo to the reaction mixture, which can complicate the purification of the desired product.

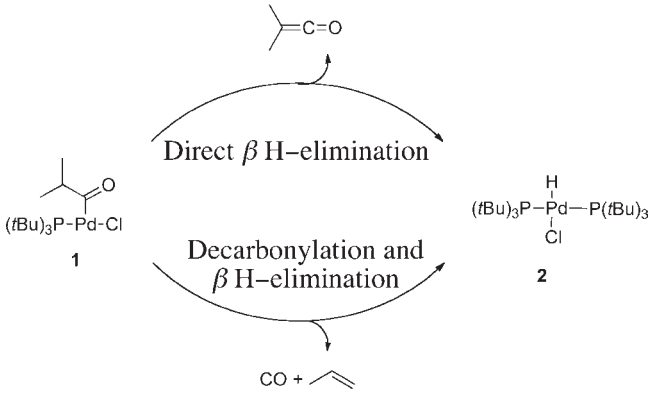
The search for alternatives to CO-gas is of great importance since they address another subject often disregarded in carbonylative chemistry, namely, stoichiometry. Apart from the industry, only in the case of the alternative CO-releasing systems mentioned above is the controlled loading of the CO-gas as a reagent evaluated. It is though surprising that the only field actually operating with substoichiometric loadings of CO on all reactions is within positron emission tomography (PET).[15] Here, the reactive component, [^{11}C]-labeled CO, is delivered in the picomolar range, and hence, transition metal induced transformations are essentially noncomparable to the reported methods discussed above. Apart from the specialized examples found within PET chemistry, essentially no literature reports are to be found on CO as the limiting reagent.[16] This topic is of interest in cases where isotopically labeled CO is applied and hence becomes a more costly reagent. A problem emerges when substoichiometric amounts of CO are applied in carbonylation chemistry; How to quantify and deliver an exact amount of CO with high efficiency? Although, the above-mentioned CO-equivalents are good candidates for this problem, a general strategy with a broad range of functional group tolerance is still required. Furthermore, only few of the already existing CO-equivalents are suitable for isotope labeling, due to their synthesis and CO-releasing capabilities.[16]

In this paper, we wish to report on our findings with the application of CO as the limiting reagent or in slight excess. Toward this purpose, a new highly efficient Pd-catalyzed decarbonylative protocol was developed releasing CO *ex situ* from pivaloyl chloride. The combination of this CO-producing reaction with a CO-consuming reaction in an isolated two-chamber system afforded high capture of the CO generated. This method was applied for the synthesis of heteroaromatic amides using 2-pyridyl tosylates in palladium-catalyzed aminocarbonylations. Further development of this class of CO-equivalents led to a stable and solid acid chloride derivative capable of releasing CO at room temperature mediated by a palladium-catalyzed decarbonylation. The straightforward synthesis and efficient CO-release from these CO-equivalents was finally applied toward [^{13}C]-carbonyl labeling in alkoxy- and aminocarbonylations mediated by palladium catalysis. Hence, indirect application of [^{13}C]-CO as the limiting reagent in the synthesis of several biologically relevant structures afforded near quantitative capture of the CO formed.

■ RESULTS AND DISCUSSION

Previous work from our group demonstrated the viability of 2-pyridyl tosylates as reactive electrophiles in Pd- and Fe-catalyzed reactions.[17] It was shown that this class of substrates represents useful coupling partners in regioselective Pd-catalyzed Mizoroki−Heck couplings, Suzuki−Miyaura cross couplings, Buchwald−Hartwig amidations, and Fe-catalyzed Kumada−Curriu cross couplings (Figure 1).[18] Interestingly, the optimized conditions

Scheme 1. Formation of 2 by Two Different Pathways



developed for the Buchwald–Hartwig amidation protocol were almost similar to those applied in the regioselective Mizoroki–Heck couplings. Knowing that a cationic palladium(II)-complex is essential for a high degree of regioselectivity in Mizoroki–Heck couplings with electron rich olefins, we contemplated that this same cationic palladium(II) intermediate might have increased affinity toward CO coordination in a possible aminocarbonylation reaction.[19] This increased affinity would originate from electronic effects but also due to the tricoordinated nature of the cationic palladium(II)-complex, formed after oxidative addition, rendering an empty site on the palladium nucleus free to CO-coordination. Not only would this provide access to 2-pyridyl amides, but at the same time reverse the installed amide functionality compared to the amidation protocol.

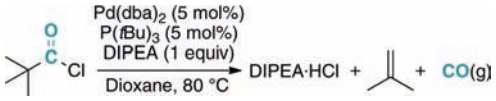
Initial screenings revealed that a catalyst formed from $Pd(dba)_2$ and D*i*PrPF in combination with CO delivered at approximately 1 atm via a balloon provided the aminocarbonylated products in yields attaining 88%.[18] However, lack of reproducibility led to a more detailed investigation of the CO-balloon delivery system, which revealed that factors governing the overall outcome of the reaction depended on small changes in the initial partial pressure (results not shown). Since a literature search revealed no useful *in situ* CO generating alternatives as the 2-pyridyl tosylate derivatives proved sensitive to strong base and high temperatures, we abandoned this setup for aminocarbonylation.

Development of a New CO-Equivalent. With the need to efficiently deliver CO to the aminocarbonylation of 2-pyridyl tosylates under mild conditions and with reproducible outcome, we became interested in the development of a new and safe CO-equivalent. Our work originated from a mechanistic study performed on the formation of a palladium(II)–hydride catalyst for the migration of olefins.[20] Mixing $P(tBu)_3$, $Pd(dba)_2$, and isobutyryl chloride in a 1:1:1 ratio at room temperature in THF resulted in the formation of the palladium(II)–hydride complex **2** (Scheme 1).[21]

A crystal structure of an acyl-palladium(II)-complex **1** was isolated and turned out to be one of the precursors for the desired palladium(II)–hydride. It was proposed that **1** could lead to the palladium(II)–hydride **2** by one of two pathways. The first being a direct β-hydride elimination of the hydrogen on the α-carbon to the carbonyl group releasing a ketene and **2**. Alternatively, a palladium(II)-induced decarbonylation followed by a β-hydride elimination would lead to **2**, propene, and CO (Scheme 1).

Interestingly, it was observed that the slow formation of **2** from **1** occurred at temperatures as low as 50 °C releasing gaseous CO

Scheme 2. Low Temperature Palladium-Catalyzed Decarbonylation of Pivaloyl Chloride



and propene, despite palladium-catalyzed decarbonylation of acyl chlorides typically requiring temperatures in the range of 120–360 °C.[22] With this in mind, we speculated that exclusion of the ketene pathway (Scheme 1) would lead exclusively to the decarbonylation pathway. This was ensured by exchanging isobutyryl chloride for an acid chloride devoid of α-hydrogens, yet retaining at least one hydrogen in the β-position. We were initially concerned that the resulting increase in sterical bulk next to the acid chloride moiety would slow the oxidative addition step, as well as the temperature requirements for the palladium-catalyzed decarbonylation step. Nevertheless, pivaloyl chloride was selected and subjected to a catalytic mixture consisting of $Pd(dba)_2$ (5 mol %), $P(tBu)_3$ (5 mol %), and a stoichiometric amount of diisopropylethylamine (DIPEA) at 80 °C. Gratifyingly, significant gas evolution was observed within minutes and subsequent ^{1}H NMR analysis of the crude reaction mixture after 20 h indicated complete consumption of the pivaloyl chloride. Furthermore, the specific shifts for isobutene residing at 4.64 ppm (sept, 2H, J = 1.2 Hz) and 1.71 ppm (t, 6H, J = 1.2 Hz) in $CDCl_3$ were observed indicating a decarbonylative pathway (Scheme 2). Addition of an internal standard to the reaction mixture and monitoring the consumption of pivaloyl chloride over time by ^{1}H NMR analysis revealed a continuous turnover reaching completion in less than 3 h using 5 mol % catalyst (see Supporting Information).

To prove that CO was produced alongside isobutene, we attempted to combine this protocol with the Pd-catalyzed aminocarbonylation of 2-pyridyl tosylates. Realizing that the aminocarbonylation of 2-pyridyl tosylates provided up to an 88% isolated yield applying a CO balloon reservoir, we speculated that performing the two catalytic reactions in parallel, only allowing the gaseous CO and isobutene to be evenly distributed above the two reactions, would provide a clean form of *ex situ* CO-delivery. This was accomplished by applying a sealed two-chamber system (**S1**) with a CO-producing chamber and a CO-consuming chamber (See Scheme 3).

The inner chamber was loaded with 2-pyridyl tosylate (**3**), *n*-hexylamine, and the optimized conditions developed for this aminocarbonylation discussed earlier. The surrounding chamber was charged with the CO-releasing system using 1.5 equiv of pivaloyl chloride when compared to the limiting 2-pyridyl tosylate (**3**). Apart from the 1:1.5 ratio between **3** and pivaloyl chloride, the reaction performed in the two separated chambers represent individual reactions. Hence, the loading of catalyst and other reagents are in relationship to the electrophile in each chamber.

The entire two-chamber system was sealed and subsequently heated to 80 °C for 20 h. Not only did this set of reactions, performed in parallel, prove that CO was actually generated from the pivaloyl chloride, but simultaneously, an excellent 87% isolated yield of the desired aminocarbonylation product **4** was secured after column chromatography. Hence, the CO-release from pivaloyl chloride in combination with the two-chamber system afforded the high incorporation of the formed

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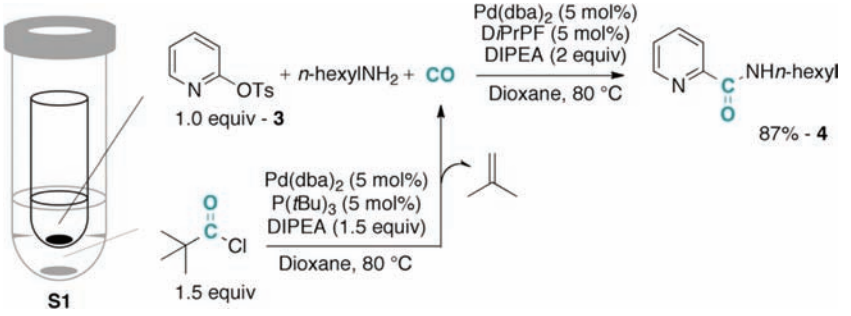
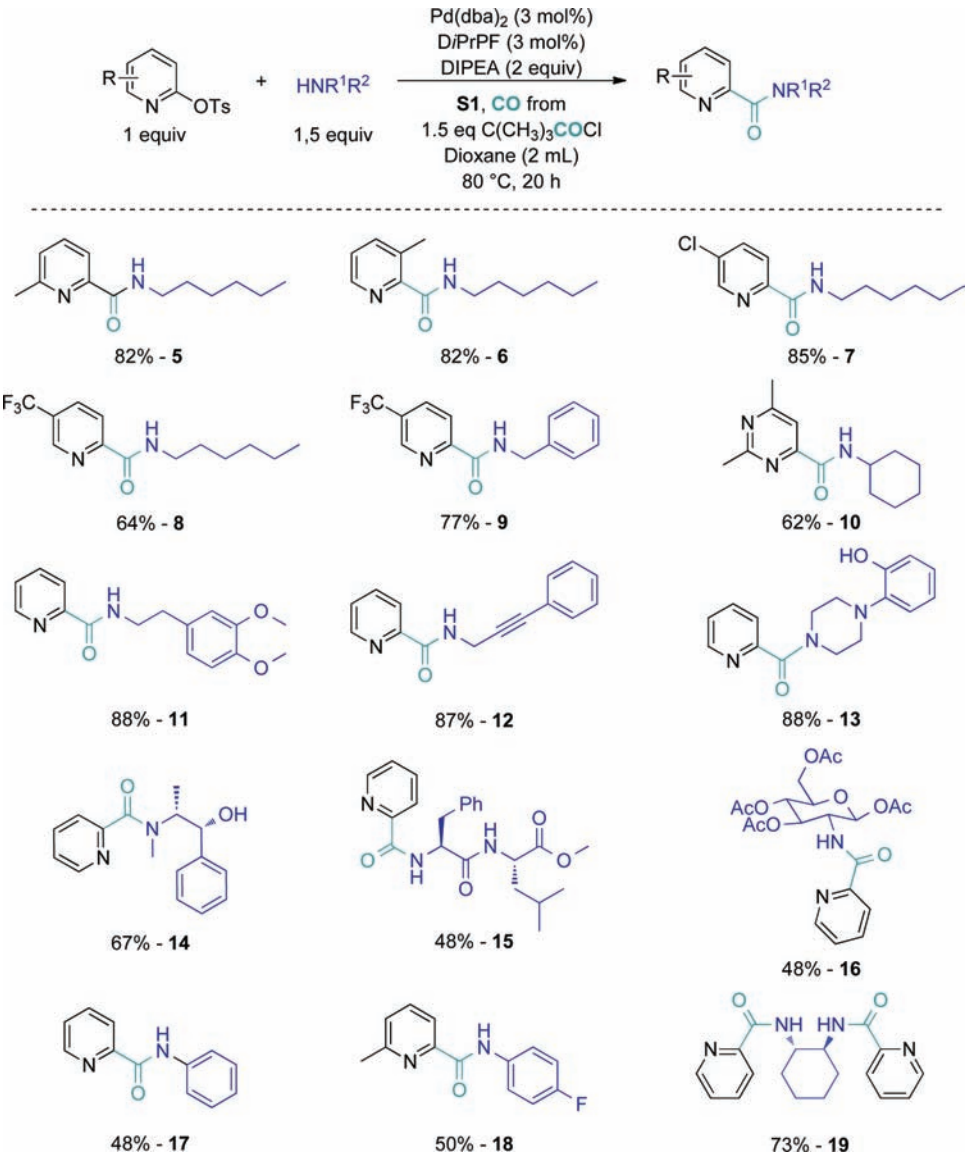
Scheme 3. Crossover of CO in a Sealed Two-Chamber System



Scheme 4. Palladium-Catalyzed Aminocarbonylation of 2-Pyridyl Tosylates[a]



[a] See Supporting Information for exact reaction conditions.

CO.[23] The presence of isobutene did not affect the progress of the catalytic reactions in either of the two chambers (The presence of isobutene will be discussed in further detail later in the manuscript). With this new CO-equivalent at our hands, we decided to investigate its application in further detail.

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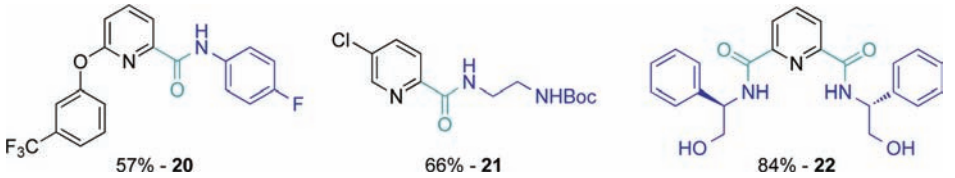
Scheme 5



Palladium-Catalyzed Aminocarbonylations of 2-Pyridyl Tosylates. A small optimization of both the CO-producing reaction and the CO-consuming aminocarbonylation reaction was performed successfully lowering the catalytic loading in both chambers to obtain a near quantitative isolated yield (96%) of **4** (see Supporting Information). These optimized conditions were then applied to test the scope of the aminocarbonylation of 2-pyridyl tosylate derivatives in combination with the two-chamber CO-releasing system. These results are depicted in Scheme 4.

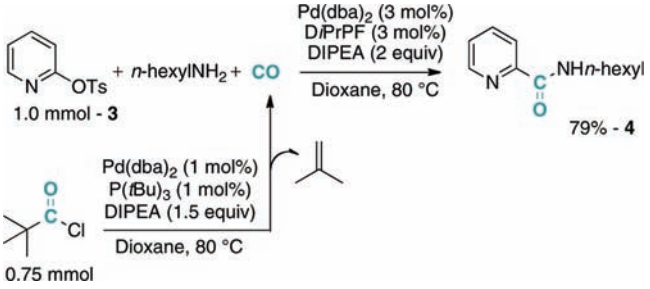
Changes in the substitution pattern of the 2-pyridyl tosylate derivatives including methyl, chlorine, and trifluoromethyl substituents afforded isolated yields from 50% to 85% (compounds **5**−**9** and **18**). However, problems emerged when further electron withdrawing groups were introduced on the pyridine core, such as competing direct amination and tosylation of the amine. The formation of the aminated byproduct and tosylated amines could in some cases be lowered by increasing the $Pd(dba)_2$/$P(tBu)_3$ catalytic loading of the CO-producing chamber in order to obtain a faster CO-release rate. Changes in the amine nucleophile did not seem to affect the reaction and both primary and secondary aliphatic amines were suitable. The presence of alcohols and phenols in the amine nucleophile also proved possible and did not affect the aminocarbonylation, thus, affording the desired compounds **13** and **14** in isolated yields of 88% and 67%, respectively. Three chiral amines proved to be successful substrates for these catalytic conditions including (−)-pseudoephedrine (**14**), a dipeptide **15**, and an acetylated glucosamine **16**. Only in the case of the dipeptide coupling was a trace epimerization observed affording a diastereomeric ratio of 93/7 as measured by ^{1}H NMR analysis. Two anilines were tested as nucleophiles and afforded the desired carbonylated coupling products **17** and **18** in a 48% and 50% isolated yield, respectively.

Finally, a double carbonylation using *trans*-1,2-cyclohexane diamine as the nucleophile provided an excellent 73% isolated yield of the C_2-symmetrical diamide **19**.

Since 4-fluoroaniline could be applied as the nucleophilic reagent, the synthesis of the known pesticide, picolinafen (**20**), was attempted (Scheme 5).[24] Because of the presence of an electron-donating group on the starting 2-pyridyl tosylate, a longer reaction time and elevated reaction temperature were required to secure a good isolated yield **20** (57%) (Scheme 5). Applying monoboc protected 1,2-diaminoethane in combination with 5-chloropyridinyl tosylate furnished the boc-protected antiparkinsonian agent, lazabemide, in a 66% isolated yield (**21**).[25] Finally, compound **22**, a precursor for the PyBox ligand, was obtained from the double carbonylation of a 2,6-pyridinyl ditosylate in an excellent isolated yield of 84%.[26]

Design of a New Solid CO-Precursor and Its Application in Substoichiometric Labeling Studies. Finally, a reaction was performed on the test system applying pivaloyl chloride as the limiting reagent and thereby using CO substoichiometrically

Scheme 6. Aminocarbonylation Applying Substoichiometric CO



(Scheme 6). Gratifyingly, the coupling product **4** could be secured in an excellent 79% isolated yield based on the pivaloyl chloride. Apart from the mechanistic aspects in applying substoichiometric CO, such a study would be of high interest in isotope labeling and attention was once again turned toward the CO-producing chamber.

Although pivaloyl chloride is an obvious choice as the CO-equivalent with regards to commercial availability, cost, and overall atom economy, it falls short of being a universal CO-precursor. First of all, being liquid with a boiling point of 105 °C at atmospheric pressure hampers its use in small-scale synthesis, purification, and handling of isotope-labeled analogues. Furthermore, the isobutene byproduct formed from this acid derivative upon CO-release induces some problems. The presence of isobutene gas in the CO-consuming chamber did not influence the outcome of the above studied aminocarbonylation, but this trend cannot be expected to be general. The inherent high reactivity of olefins under a wide variety of different reaction conditions would limit the diversity of the types of reactions, which can be performed in the CO-consuming chamber.[27] Finally, the formation of isobutene adds to the overall pressure formed inside the closed two-chamber system during CO-release, rendering pivaloyl chloride an inadequate choice for further studies.

To solve these issues, we set out to identify an alternative CO-precursor in the form of an acid chloride with the following four requirements: (a) the byproduct formed upon CO-release must be nonvolatile in order to avoid cross-contamination to the CO-consuming chamber; (b) in applications of isotope-labeling, the isotope labeled carbonyl group can be introduced at a late stage in the synthesis of this precursor; (c) the CO-precursor should be a crystalline stable solid, which is easy to synthesize on large scale; and finally, (d) the CO precursor can be resynthesized from the alkene product after decarbonylation and β-hydride elimination preserving a reasonable atom economy. To this end, compound **25** was selected for subsequent studies (Scheme 7). The synthesis of **25** starts from commercially available 9-fluorenone following a literature procedure.[28] Initially, 9-fluorenone is methylated using MeMgI forming **23**, which is then converted into 9-methyl-9*H*-fluorene by an acid catalyzed dehydration in refluxing glacial acetic

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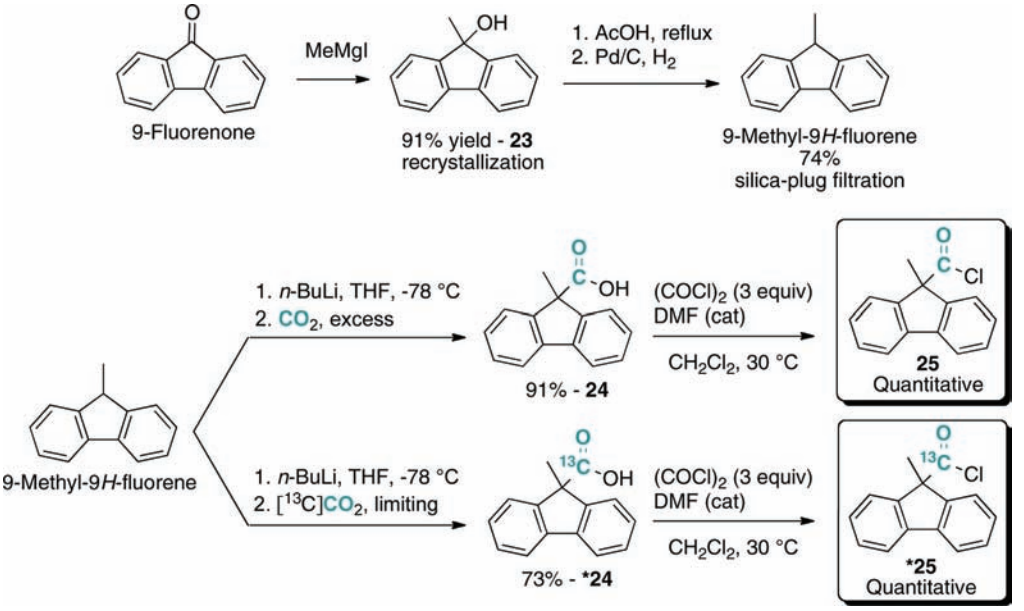
Scheme 7. Preparation of 25 and *25

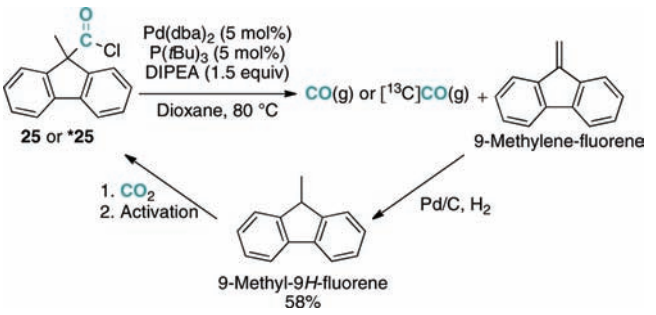


acid and ensuing hydrogenation using Pd/C and H_2 (1 atm - balloon) in a one-pot procedure. 9-Methyl-9*H*-fluorene was obtained in a 67% isolated yield (2 steps) starting from 20 g of 9-fluorenone (111 mmol). 9-Methyl-9*H*-fluorene was subsequently lithiated using *n*-BuLi, followed by CO_2 capture in cold THF. Applying CO_2 in excess resulted in an isolated yield of 91% of the acid precursor **24**. 9-Methyl-9*H*-fluorene was also used for the capture of [^{13}C]-CO_2 applied as limiting reagent, resulting in a 73% isolated yield of ***24**. Compounds **24** and ***24** were then transformed quantitatively into their acid chloride derivatives **25** and ***25** using oxalyl chloride and a catalytic amount of DMF in CH_2Cl_2 at 30 °C. Both **25** and ***25** are stable and easy to handle solids at room temperature, which can be recrystallized from CH_2Cl_2/pentane or Et_2O/pentane mixtures if needed.

Upon CO-release, **25** and ***25** formed the nonvolatile 9-methylene-fluorene, which upon Pd-catalyzed hydrogenation regenerated 9-methyl-9*H*-fluorene in a 58% isolated yield (average of combined 9-methylene-fluorene formed from 43 carbonylation reactions), representing the common precursor for **25** and ***25** (Scheme 8). With this new CO-equivalent in hand, we set forth to investigate its application in palladium-catalyzed carbonylation reactions using CO as the limiting reagent.

To evaluate the substoichiometric CO reactions, we decided to apply a palladium-catalyzed aminocarbonylation reaction other than those developed for the 2-pyridyl tosylates, in order to avoid the nonspecific side reactions of direct amination and tosylation of the amine nucleophile, which both deplete the electrophilic reagent. A new two-chamber system (**S2**) was designed keeping the total volume almost identical as before (Scheme 9; see Supporting Information) for the ease of handling and to ensure proper stirring. After a short optimization, the aminocarbonylation of 4-iodoanisole with *n*-hexylamine using $Pd(dba)_2$, PPh_3 and TEA in dioxane at 80 °C proved highly efficient for CO capture from **25** in combination with the sealed two-chamber system (Scheme 9).

Scheme 8. CO-Release and Regeneration of 25 and *25



Once again, apart from the 1:1.5 ration between **25**/***25** and 4-iodoanisole, the reaction performed in the two separated chambers represent individual reactions. Hence, the loading of catalyst and other reagents is in relationship to the electrophile component in each chamber.

The new CO-precursor **25** did deliver the CO required for the aminocarbonylation and ^{1}H NMR analysis of the crude reaction mixture in the CO-producing chamber showed full conversion of **25** into 9-methylene-fluorene after 20 h (see Supporting Information). To our delight, the coupling product **26** was isolated in a near quantitative yield (96%) based on limiting **25**, and hence, limiting CO-gas formed for the reaction. The high yield of isolated **26** also indicates a near stoichiometric and clean conversion of the **25** precursor into 9-methylene-fluorene. In comparison, **26** was isolated in an 84% isolated yield when pivaloyl chloride was applied as the CO-source. Whether this difference in yield is due to the rate at which the two different CO-precursors release CO for the subsequent palladium-catalyzed aminocarbonylation in the CO-consuming chamber or if the conversion of pivaloyl chloride into CO is less efficient compared to **25** remains to be explored. Finally, when the isotope labeled ***25** was applied, ***26** was secured in a comparable 96% isolated yield with >95% incorporation of [^{13}C]-CO as measured by ^{1}H NMR proving the

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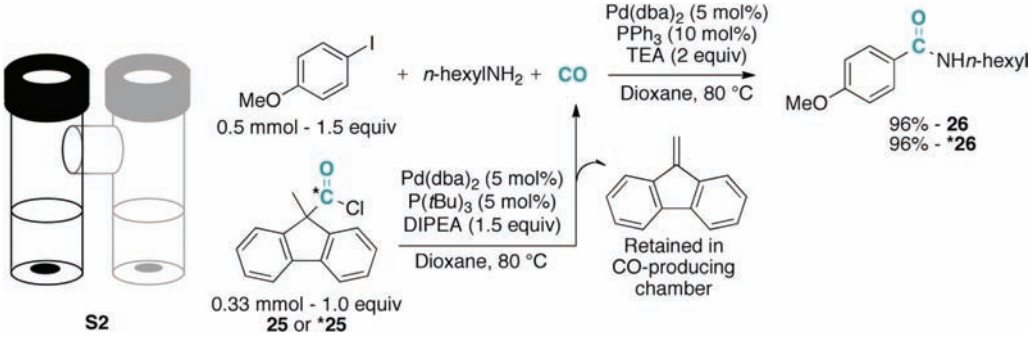
Scheme 9. Test Reaction Using 25 or *25 as CO-Precursor



concept of this labeling technique.[23] The reactions depicted in Scheme 9 clearly indicate that CO can be applied as the limiting reagent. Furthermore, gas-equilibria between the two reaction chambers and mixtures are seemingly fast and nonproblematic.

To test the full scope of the CO-precursors **25** and ***25** in combination with the two-chamber system, we applied the methodology in the synthesis of a variety of biologically relevant structures carrying an amide or ester functionality (Table 1). The synthetic route to these compounds were designed with the aim of performing the aminocarbonylation in the final step or on a late stage intermediate in order to obtain maximum utilization of the labeled precursor. The yields in Table 1 are based on CO as the limiting reagent and test reactions were performed using **25** prior to applying labeled ***25**. All the aryl iodides were aminocarbonylated using the $Pd(dba)_2/PPh_3$ catalytic system in dioxane (entries 1−3, 5 and 6), and conditions used in the example illustrated in Scheme 9. This furnished the structurally related compounds, metaclopramide[29] (**31**) and bromopride[30] (**32**) (entries 5 and 6), in isolated yields of 63% and 65%, respectively. Together with itopride[31] (**29**) in entry 3, these compounds represent gastroprokinetic drugs applied for the treatment of irritable bowel syndrome, acid reflux disease, gastroparesis, and others. Gratifyingly, upon use of the CO precursor ***25**, their [^{13}C]-CO labeled analogues were isolated in yields ranging from 62 to 89% (entries 3, 5, and 6). The efficiency of two other iodides was tested with both a primary and a secondary amine affording *N*-(2-(diethylamino)ethyl)nicotinamide (**27**), and the piperazine derivative **28** (entries 1 and 2) in excellent isolated yields of 83% and 86%, respectively.[32] The latter is a compound patented by GlaxoSmithKline for its effect on the histamine H_3 receptor. Their [^{13}C]-CO labeled counterparts were obtained in a near 90% isolated yield for both cases, simply by changing to the isotope-labeled CO-precursor.

Aryl bromides were also tested as electrophiles, but preliminary studies revealed that a change of catalytic conditions for the palladium-catalyzed aminocarbonylation was required. Modified conditions of those reported by Buchwald[6a] and Beller[6j] using XantPhos or CataCXium A in toluene at 80 °C proved useful (for specific reaction conditions see Supporting Information). At this stage it should be mentioned that the conditions applied for the aminocarbonylations are virtually unoptimized. To avoid minimal solvent exchange between the two chambers, toluene was applied as the solvent in the CO-producing chamber. Applying these new conditions, compound **30**, belonging to the ampakine-class of compounds, was synthesized in an 83% isolated yield.[15,33] An excellent yield of 95% was obtained for the isotope-labeled ***30** when applying ***25** (entry 4). Differences in isolated yield between these two reactions could be related to the stability of the palladium catalyst applied in the aminocarbonylation. Toward the end of the reaction, when nearly all the CO has been consumed, the stability of the palladium complex formed after oxidative addition must be high in order to avoid catalyst decomposition.[6a,34] It should be noted that, since an excellent 95% isolated yield of ***30** was secured, a near quantitative CO-release occurs in the CO-producing chamber despite the change in solvent from dioxane to toluene.

Two intramolecular aminocarbonylations where also attempted affording an 84% yield of **33** (75% yield of ***33**),[35] representing the core of the PARP1 inhibitor family, and a 79% yield of **34** (80% yield of ***34**),[13m] a precursor for loxapine. Finally, an alkoxycarbonylation was attempted applying 2-(diethylamino)ethanol as the nucleophilic counterpart and DMAP as an acyl transfer reagent. This afforded butoxycaine (**35**), a local anesthetic, in a good 89% isolated yield.[36] Once again, simply by changing to ***25** in the CO-generating chamber resulted in a good isolated yield (91%) of [^{13}C]-labeled butoxycaine.

During the aminocarbonylations using **25**, visual inspection of the reactions suggested that the CO-release from this precursor commenced at a lower temperature compared to pivaloyl chloride, which did not provide CO-release below 50 °C. Formation of bubbles occurred at room temperature which was surprising since catalytic palladium-catalyzed decarbonlyations usually require temperatures well above 100 °C.[22] Two room temperature aminocarbonylations were performed with *n*-hexylamine and *p*-methoxyphenyl iodide using protocols developed by Kondo and Lizuka in order to capture the CO formed at this unusual low temperature (Scheme 10).[37]

Applying DABCO as the base afforded a good 86% isolated yield of the amide **26**. On the other hand, switching to the use of DBU promoted double carbonylation at room temperature, furnishing **36** in a 68% isolated yield with only a 7% yield of **26**. To the best of our knowledge, this is the first time an efficient palladium-catalyzed decarbonylation of an acid chloride is reported at room temperature. These results, in combination with the fact that CO-release from pivaloyl chloride, **25**, and ***25** can be performed in all solvents tested so far including toluene, dioxane, and THF prove the broad utility of this new method.

■ CONCLUSION

Work related to the palladium-catalyzed aminocarbonylation of 2-pyridyl tosylates led us to identify pivaloyl chloride as a new and safe CO-source. Release of CO from this acid chloride was mediated by a palladium-catalyzed decarbonylation performed at 80 °C. Subsequent β-hydride elimination releasing isobutene

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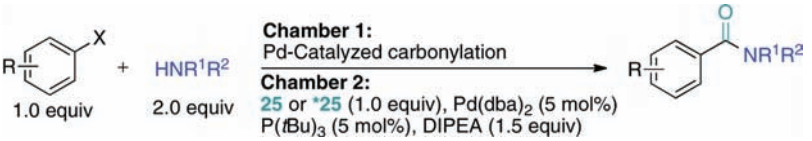
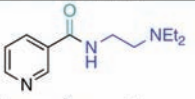
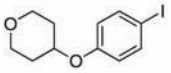
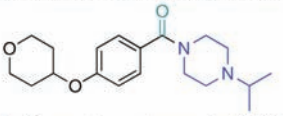
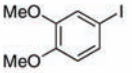
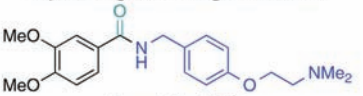
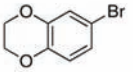
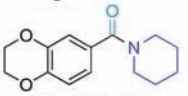
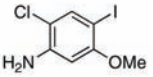
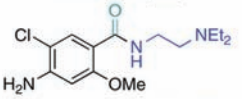
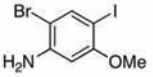
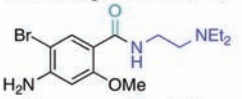
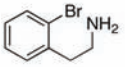
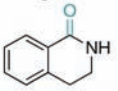
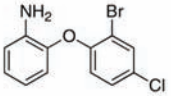
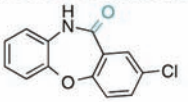
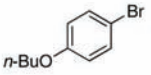
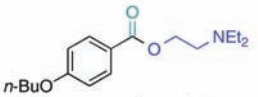
Table 1. Palladium-Catalyzed Carbonylations Using 25 and *25[a]



Entry	(Het)Ar-X	Product	25[b]	*25[b]
1		 PET Tracer for melanoma (**27**)	86%	87%
2		 H_3-Receptor antagonist (**28**)	83%	90%
3		 Itopride (**29**)	94%	89%
4		 CX-546 (**30**)	83%	95%
5		 Metaclopramide (**31**)	63%	62%
6		 Bromopride (**32**)	65%	66%
7		 Core of PARP1 inhibitors (**33**)	84%	75%
8		 Loxapine precursor (**34**)	79%	80%
9		 Butoxycaine (**35**)	89%	91%

[a] For full detailed procedures, see the Supporting Information. [b] Yield using 1.0 equiv CO precursor .

followed by a base induced reductive elimination regenerated the CO-releasing catalyst. The coupling reactions were performed in parallel in an interconnected and sealed two-chamber system in order to cleanly and efficiently deliver the CO-gas formed. This new system was applied in the aminocarbonylation of 2-pyridyl tosylate derivatives providing good to excellent yields of the desired products using only 1.5 equiv of pivaloyl chloride as the CO-precursor. Furthermore, applying pivaloyl chloride as the limiting reagent resulted also in good yields of the 2-pyridyl amide. To apply this methodology to the isotope labeling of aryl amides, an alternative acid chloride **25** and its [^{13}C]-labeled counterpart ***25** were prepared as stable, crystalline, and easy to synthesize CO-precursors. Applying **25** and ***25** as the limiting reagents with the two-chamber system led to high incorporation of the *ex situ* CO formed in the synthesis of several pharmaceutically relevant compounds and their [^{13}C]-labeled derivatives by palladium-catalyzed aminocarbonylation. The high degree of CO-capture was in all cases accredited to the application of the

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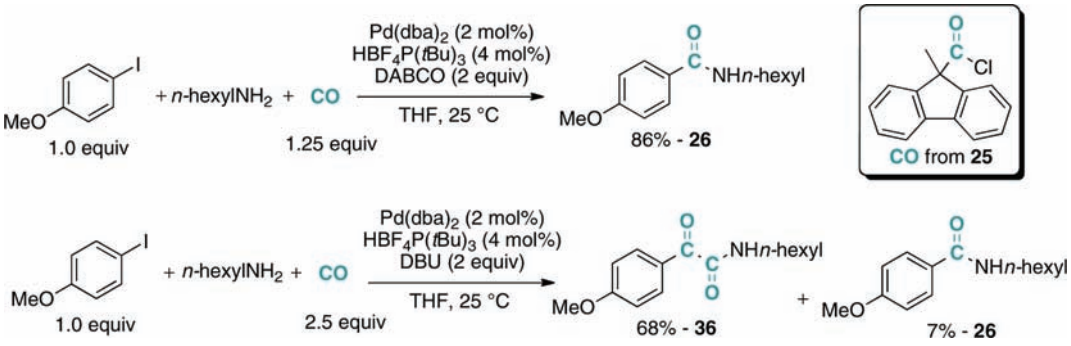
Scheme 10. Room Temperature Palladium-Catalyzed Decarbonylation of 25



sealed interconnected two-chamber system that provides a clean source of CO for the consuming reaction. Further studies on the CO-releasing capabilities of **25** revealed that the palladium mediated CO-release occurred as low as room temperature for this specific acid chloride.

This new protocol applying acid chlorides as CO-precursors in combination with the two-chamber system will be of high value for synthetic chemists, not only as a new source of a safe and storable CO gas, but also because of its ease in handling and straightforward use in CO related chemistry, including isotope labeling studies. Furthermore, compared to the numerous CO-equivalents developed for *in situ* release, this new protocol holds the advantage of being independent of the CO-consuming reaction thereby expanding its scope in CO-related chemistry. With the possibility to control the release of carbon monoxide by altering the catalytic loading and the release temperature, this method also provides the opportunity to potentially generate a constant delivery of CO-gas thereby avoiding high-pressure equipment. Further studies toward the implementation of this methodology in the field of [^{14}C]-CO and [^{11}C]-CO labeling are currently being conducted and will be reported in due time.

EXPERIMENTAL SECTION

General Methods. Solvents were dried according to standard procedures. Flash chromatography was performed on silica gel 60 (230−400 mesh). The chemical shifts of the NMR spectra are reported in parts per million (ppm) relative to the solvent residual peak.[38] MS spectra were recorded on a LC TOF (ES) apparatus. All purchased chemicals were used as received without further purification.

Aminocarbonylation of 2-Pyridyl Tosylates Using Pivaloyl Chloride. *5-Chloro-N-hexylpicolinamide (**7**).* Pd(dba)$_2$ from a 0.01 mg·μL^{-1} stock solution in dioxane (432 μL, 7.5 μmol), P(tBu)$_3$ from a 0.02 mg·μL^{-1} stock solution in dioxane (75.9 μL, 7.5 μmol), distilled pivaloyl chloride (92.4 μL, 750 μmol), distilled diisopropylethylamine (131 μL, 750 μmol), and 2.25 mL of dioxane in the external chamber and 2-(5-chloro)pyridinyl tosylate (141.9 mg, 500 μmol), Pd(dba)$_2$ from a 0.01 mg·μL^{-1} stock solution in dioxane (863 μL, 15 μmol), D*i*PrPF from a 0.02 mg·μL^{-1} stock solution in dioxane (314 μL, 15 μmol), hexylamine (99.2 μL, 750 μmol), diisopropylethylamine (174 μL, 1.0 mmol), and 750 μL of dioxane in the internal chamber. Purification of the residue by column chromatography on silica gel using CH_2Cl_2 to CH_2Cl_2/EtOAc (100/3) provided compound **7** as a pale yellow oil (85%, 102 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 2.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.89 (bs, 1H), 7.79 (dd, J = 8.3 Hz, J = 2.3 Hz, 1H), 3.43 (q, J = 6.9 Hz, 2H), 1.60 (quin, J = 7.2 Hz, 2H), 1.41−1.24 (m, 6H), 0.87 (t, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 148.2, 146.9, 137.0, 134.7, 123.1, 39.5, 31.4, 29.5, 26.6, 22.5, 14.0. HRMS (ESI) $C_{12}H_{17}ClN_2O$ [M + Na$^+$]; calculated 263.0927, found 263.0935.

Aminocarbonylation of Aryl Halides Using 25/*25. *Itopride (**29**).* In a glovebox under argon, to chamber 1 of two-chamber system **S2** was added Pd(dba)$_2$ (9.6 mg, 0.017 mmol), **25** or ***25** (81.0 mg, 0.333 mmol), dioxane (3 mL), P(tBu)$_3$ (from stock solution, 0.01 mg μL^{-1}, 337 μL, 0.0167 mmol), and diisopropylethylamine (87 μL, 0.50 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal.

In a glovebox under argon, to chamber 2 of two-chamber system **S2** was added Pd(dba)$_2$ (14.4 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 4-iodoveratrole (132 mg, 0.5 mmol), dioxane (3 mL), 2-(4-(aminomethyl)phenoxy)-*N*,*N*-dimethylethanamine (194 mg, 1.0 mmol), and triethylamine (139 μL, 1.0 mmol). The chamber was sealed with a screwcap fitted with a Teflon seal. The loaded two-chamber system was heated to 80 °C for 20 h. The title compound **29** was obtained after flash chromatography (increasing polarity from 60% to 20% EtOAc in a mixture of MeOH/CH_2Cl_2 (1:1) as eluent) and subsequent washing of a CH_2Cl_2 solution of the compound with saturated aqueous Na_2CO_3, as a colorless solid (111.7 mg, 0.312 mmol, 94% from **25**). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, J = 2.0 Hz, 1H), 7.29−7.25 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, J = 6.35 (br s, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.06 (t, J = 6.0 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 2.73 (t, J = 5.6 Hz, 2H), 2.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.9, 158.1, 151.5, 148.8, 130.6, 129.1 (2C), 127.0, 119.5, 114.6 (2C), 110.6, 110.1, 65.9, 58.2, 55.9, 55.9, 45.8 (2C), 43.4. HRMS $C_{20}H_{26}N_2O_4$ [M + Na$^+$]; calculated: 381.1790, found: 381.1794

*[^{13}C]-Itopride (*29).* Same procedure as **29** using ***25**. ***29** was obtained as a colorless solid (106.4 mg, 0.296 mmol, 89% from ***25**). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (dd, J = 4.0 Hz, J = 2.0 Hz, 1H), 7.30−7.25 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 6.84 (dd, J = 8.4 Hz, J = 0.8 Hz, 1H), 6.45−6.38 (m, 1H), 4.56 (dd, J = 5.6 Hz, J = 3.2 Hz, 2H), 4.05 (t, J = 5.6 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.33 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.9 (^{13}C-enriched), 158.2, 151.6, 148.8 (d, J = 3.2 Hz), 130.7, 129.1 (2C), 127.1 (d, J = 66.1 Hz), 119.5 (d, J = 2.4 Hz), 114.7 (2C), 110.6, 110.2, 66.0, 58.3, 55.9 (2C), 45.9 (2C), 43.5. HRMS $C_{19}{}^{13}CH_{26}N_2O_4$ [M + H$^+$]; calculated: 360.2004, found: 360.2006.

ASSOCIATED CONTENT

Supporting Information. Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. Glassware characteristics for **S1** and **S2**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
ts@chem.au.dk

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