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$Pd(OH)_2/C$, a Practical and Efficient Catalyst for the Carboxylation of Benzylic Bromides with Carbon Monoxide.

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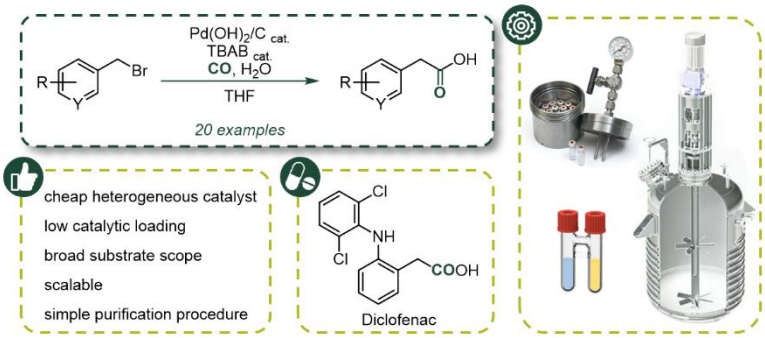
Dedicated to the memory of Dr. Alexis Coste, a talented, energetic and energizing chemist gone too soon.



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ABSTRACT. A simple, efficient, cheap and broadly applicable system for the carboxylation of benzylic bromides with carbon monoxide and water is reported. Upon simple reaction with only 2.5 wt% of Pearlman's catalyst and 10 mol% of TBAB in THF at 110 °C for 4 hours, a range of benzylic bromides can be smoothly converted to the corresponding arylacetic acids in good to excellent yields after simple extraction and acid-base wash. The reaction was found to be broadly applicable, scalable and could be successfully extended to the use of *ex situ*-generated carbon monoxide and applied to the synthesis of the non-steroidal anti-inflammatory drug diclofenac.

KEYWORDS: palladium catalysis, heterogeneous catalysts, carboxylation, benzylic bromides, benzylic acids, arylacetic acids, carbon monoxide.

1. INTRODUCTION

Arylacetic (or benzylic) acids are key molecules in organic synthesis. In addition to their use in a number of chemical transformations, they are also important molecules in the food industry – phenylacetic acid itself being an important food additive with caramel, floral and honey taste –, or in the cosmetic industry where phenylacetic acid is commonly used for its honey-like odor even at low concentrations. This moiety is also found in a plethora of well-known drugs such as ibuprofen **1**, naproxen **2** and diclofenac **3**, major non-steroidal anti-inflammatory drugs, or olopatadine **4**, a medication used to decrease the symptoms of allergic conjunctivitis and rhinitis (Figure 1). Arylacetic acid derivatives are in addition commonly found in a number of drugs that include penicillin G **5**, an antibiotic, clopidogrel **6**, an antiplatelet medication, or methyl phenidate

7, a drug used to treat attention deficit hyperactivity disorder and narcolepsy. Arylacetic acids and their derivatives are also commonly utilized in the agrochemical sector, representative examples including 1-naphthaleneacetic acid **8**, a synthetic plant hormone found in many commercial plant rooting horticultural products, or fenvalerate **9**, a pyrethroid insecticide.

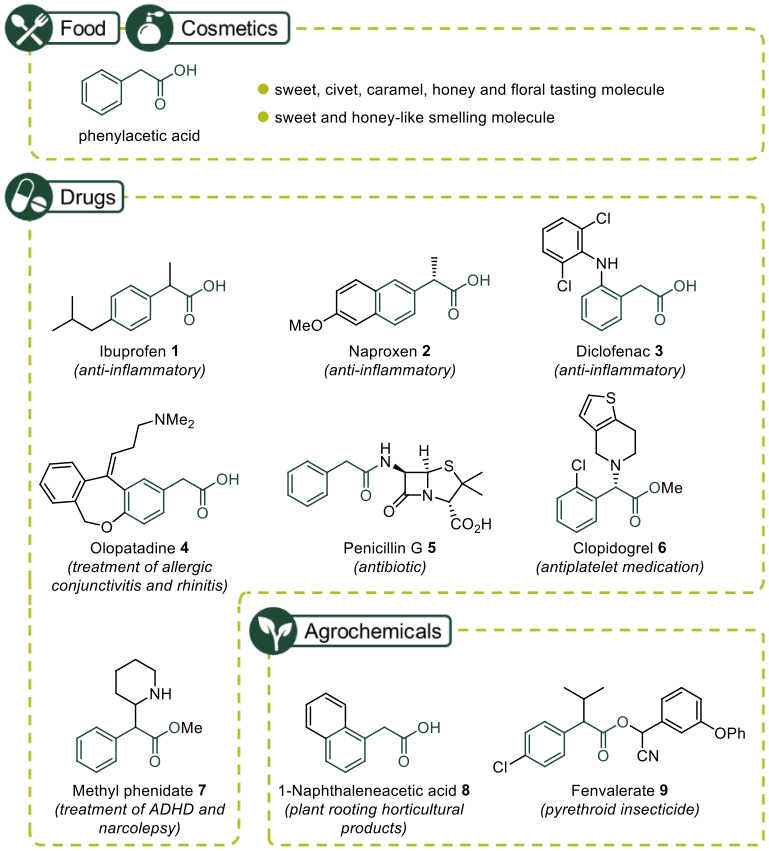


Figure 1. Representative arylacetic acid derivatives from the food, cosmetic, medicinal and agrochemical indutries.

While benzylic acids can be produced by a number of methods from a range of precursors, which includes the oxidation of homobenzylic alcohols, the hydrocarboxylation of styrenes[1,2] or the more recently developed α-arylation of aliphatic carboxylic acids[3] and direct (photo)carboxylation of benzylic C-H bonds,[4] all these reactions suffer from limitations in terms

of precursors availability, scope, efficiency and/or selectivity and the precursors of choice, notably from an industrial perspective, remain the corresponding benzylic bromides.[5] Traditionally, they have indeed been converted in two steps to the corresponding benzylic acids by cyanation followed by hydrolysis. Despite the obvious limitations of this sequence in terms of toxicity and efficiency, it is still however a method of choice commonly utilized for the large scale preparation of a range of arylacetic acids, notably in industrial settings. The main alternative processes for the conversion of benzylic bromides to the corresponding benzylic acids include their transformation to benzylic Grignard reagents and their further reaction with carbon dioxide, a reaction that suffers from significant competitive dimerization of the starting benzylic bromide due to a facile Wurtz coupling and that is not especially practical –[5,6] even if benzylic bromides can now be directly carboxylated with carbon dioxide by various catalytic[7] or electrochemical processes[5] –, their Nef-type oxidation with sodium nitrite and acetic acid[8] or their palladium-catalyzed carboxylation with chloroform under basic conditions[9] or with formic acid.[10] A more appealing alternative in terms of cost, efficiency, generality and atom economy lies in their catalytic carboxylation with carbon monoxide, a reaction that can be catalyzed by a range of acids and metals:[5] while acid catalysts suffer from harsh conditions and limited substrate scope, various metals have been shown over the years to efficiently mediate the conversion of benzylic halides and carbon monoxide to the corresponding acids. They include cobalt,[11] iron,[12] rhodium,[13] nickel,[14] ruthenium,[15] and palladium,[16] the latter being usually more efficient, and therefore, preferred. If a range of palladium-based catalysts have been shown to promote the carboxylation of benzylic halides to benzylic acids with carbon monoxide, a number of them however still suffer from competitive reduction or dimerization of the starting halides[5] and no

general heterogeneous palladium catalyst has been reported to date,[16] despite a strong potential in terms of catalyst separation and recovery as well as product contamination. In an attempt to address these limitations and based on our combined interests in metal catalysis[17] and process chemistry,[18] we became interested in developing an efficient, cheap and general heterogeneous catalytic system for the carboxylation of benzylic bromides with carbon monoxide and we report herein the results of our investigations.

2. RESULTS AND DISCUSSION

Optimization of the heterogeneous palladium-based catalytic system. We initiated our studies by evaluating the efficiency of a range of heterogeneous palladium catalysts for the carboxylation of a model benzylic bromide, *p-tert*-butyl-benzyl bromide **10a**, which was selected as the substrate for the optimization for its high boiling point and since its carboxylation yields to non-volatile *p-tert*-butyl-phenylacetic acid **11a**. This model substrate was therefore reacted with carbon monoxide (10 bar) in the presence of 10 wt% of the heterogeneous catalyst (5 wt% Pd), except in the case of $Pd(OH)_2/C$ (20 wt% Pd) for which 2.5 wt% were used, 10 mol% of tetrabutylammonium bromide (TBAB) – an additive commonly used in ligand-free palladium-based catalytic systems to improve catalyst activity and stability[19] and which had been in addition shown to be efficient when used as a solvent for the carboxylation of benzyl halides –[16n] and 4 equiv. of water in 50 volumes of THF at 110 °C for 4 hours. Yields, conversions and proportions of *p-tert*-butyl-toluene **12a** and *p-tert*-butyl-benzyl alcohol **13a**, the only formed byproducts resulting from competing reduction and hydrolysis of **10a**, respectively, were calculated by ^1H

NMR analysis of the crude reaction mixtures after filtration of the catalyst: results from these studies are shown in Figure 2 and reveal that while most studied catalysts (Pd/C, $Pd(OH)_2/C$, Pd black, $Pd/BaSO_4$, $Pd/CaCO_3$ and Pd/Al_2O_3) promoted the reaction, Pd/C was found to be quite efficient but higher yields and conversions were obtained with $Pd(OH)_2/C$ and $Pd/BaSO_4$. Due to the lower cost of the former, it was therefore selected as the optimal catalyst for the rest of the optimization. In all cases, minor amounts of reduced **12a** and hydrolyzed **13a** products were detected in the crude reaction mixtures.

Having determined the superiority of Pearlman's catalyst, we next moved to screening the influence of the solvent utilized for the carboxylation, the solvents for this second step of the optimization being selected on the basis of their miscibility with water and of their use on a larger scale. As evidenced by results summarized in Figure 2, the solvent was found to have a dramatic impact on the outcome of the reaction: while almost no reaction occurred in toluene, poor conversions were observed in dioxane and acetonitrile. A higher conversion was achieved in DMF but with a significant increase of competing hydrolysis – a reaction that was found, quite logically, to be the main reaction when the carboxylation was performed in water – due to the too high polarity of this solvent. The best result was actually obtained with the solvent we had chosen at the beginning of our studies, THF, which was therefore selected as the solvent of choice for the carboxylation.

A broad range of additives commonly utilized in palladium-catalyzed reactions was next evaluated. While the presence of an additive was found to be crucial for the carboxylation to occur, no product being basically formed in the absence of additive, tetrabutylammonium salts

had a positive impact on the outcome of the reaction, except in the case of tetrabutylammonium iodide which gave a poor conversion and an important amount of competing hydrolysis, a side reaction that could be facilitated by an *in situ* Finkelstein reaction. Among all tetrabutylammonium salts evaluated, TBAB gave the best result. Tetrabutylphosphonium hydroxide was also found to have a positive impact on the reaction but, as with TBAOH, also favored the hydrolysis and tetramethylammonium salts, which were evaluated because of their higher stability since they cannot undergo degradation through a Hofmann elimination, were found to be inefficient, mostly due to their poor solubility in THF. Triphenylphosphine was also shown to be a suitable additive but a low conversion and a higher amount of reduced product **12a** were noted in this case; increasing the amount of this additive in order to reach a higher conversion proved to be successful but a too high proportion of competing hydrolysis to compound **13a** was still observed. As a note, increasing the loading of TBAB, which was selected as the best additive, did not result in a higher yield.

Having selected the best palladium catalyst, additive and solvent, we next evaluated the influence of the concentration by performing the reaction in more diluted and concentrated media. As highlighted in Figure 2, the concentration did not have a major influence on the reaction, too high concentrations however resulting in higher amounts of hydrolysis while too low concentrations favored the reduction, the best compromise relying on the use of 40 volumes of THF. We finally focused on the impact of the last reaction parameters: the pressure of carbon monoxide, the temperature and the reaction time. Decreasing the pressure to 9, 7 or 5 bar resulted in decreased yields and lower conversions while performing the reaction at 60 °C instead of 110 °C (not shown) brought the conversion down to 11%. Finally, a longer reaction time (not

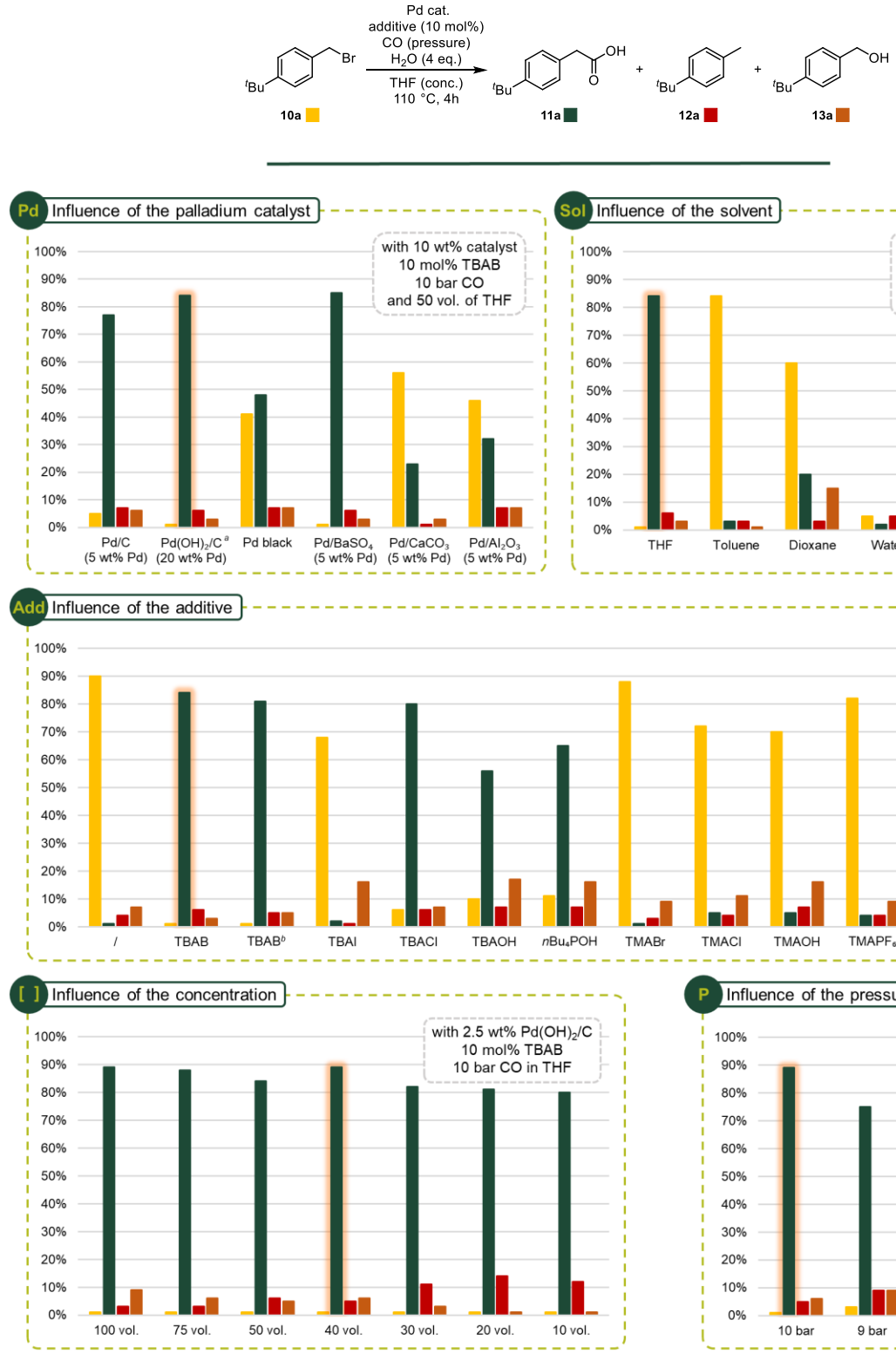
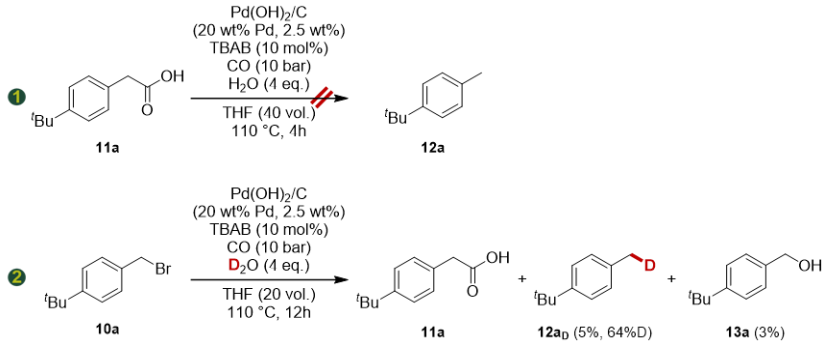


Figure 2. Optimization of the palladium-catalyzed carboxylation. [a] *with 2.5 wt% Pd(OH)$_2$/C.* [b] *with 20 mol%.*

shown) was found to be detrimental since performing the reaction overnight in place of for 4 hours gave a lower yield (76% *vs* 89%) and a higher amount of reduced product **12a** (18% *vs* 5%), presumably due to a decarboxylation of the desired product **11a** with prolonged reaction times.

At this stage, we briefly focused our efforts on understanding the origin of the formation of the reduced product **12a**, which could be useful to potentially minimize its proportion. One possibility that might account for the formation of this byproduct would involve the decarboxylation of acid **11a**; this hypothesis could however be easily discarded since upon reacting *p-tert*-butyl-phenylacetic acid **11a** under the standard reaction conditions for 4 hours, it could be fully recovered and ^{1}H NMR analysis of the crude mixture revealed the absence of *p-tert*-butyl-toluene **12a** (Scheme 1, eq. 1). THF and TBAB being hardly reducing agents in palladium-catalyzed reactions and the reduction being in addition also observed with other solvents and additives, we therefore wondered if the reduction did not result from the water-gas shift reaction between carbon monoxide and water that would produce molecular hydrogen within the reaction mixture. The carboxylation of *p-tert*-butyl-benzyl bromide **10a** was thus performed with deuterated water, ^{1}H NMR analysis of the crude reaction mixture revealed the formation of deuterated reduced product **12a$_D$** with a good level of deuteration (Scheme 1, eq. 2), therefore suggesting that the reduction was due to the reagents needed for the carboxylation, *i.e.* carbon monoxide and water, minimizing the formation of the reduced product being therefore highly challenging if not impossible.



Scheme 1. Origin of the competing reduction of benzylic bromides.

Screening all parameters of the carboxylation therefore resulted in an optimal system for the carboxylation based on the use of 2.5 wt% of $Pd(OH)_2/C$ (20 wt% Pd), 10 mol% of TBAB, 4 equiv. of water under 10 bar of carbon monoxide in 40 volumes of THF at 110 °C for 4 hours. These conditions resulted in a ^1H NMR yield of 89% for the desired benzylic acid **11a** with a full conversion and around 5% of reduced **12a** and hydrolyzed **13a** products. The desired acid could be easily isolated in a pure form by filtration of the crude reaction mixture over a plug of Celite®, concentration, extraction with a 1M aqueous solution of sodium hydroxide which was washed with pentane to remove all byproducts, acidification with a 10% aqueous solution of hydrochloric acid and extraction with diethyl ether. Using this simple and standard procedure, an isolated yield of 77% could be obtained.

Having in hand the optimized conditions and work-up procedure, we then assessed the scope and limitations of our system for the palladium-catalyzed carboxylation of a series of benzylic bromides. Results from these studies will now be overviewed.

Scope and limitations of the $Pd(OH)_2/C$-catalyzed carboxylation of benzylic bromides. To test the efficiency of our procedure, a set of benzylic bromides **10** with representative electronic and

steric properties was therefore subjected to our optimized conditions: results from this study are summarized in Figure 3. As evidenced by these results, our procedure was found to be rather general and the desired arylacetic acids **11** could be obtained in good to excellent yields in most cases and without the need for further purification after the acid-base wash. *Para*-, *meta*-, and even *ortho*- substituted benzylic bromides were shown to be readily carboxylated, the former giving however a superior yield. Electron-rich and electron-poor substrates worked equally well, providing the corresponding arylacetic acids **11a**-**f** and **11g**-**n** in good yields. A range of substituents were tolerated, including a benzyl ether (**11f**), a nitrile (**11g**) and a *tert*-butyl ester (**11i**) while a more labile ethyl ester (**11h**) was cleaved under the reaction conditions and a nitro group (**11j**) gave a poorer yield, presumably due to its competing reduction. Interestingly, an aromatic chloride (**11m**) and even a bromide (**11n**) were stable under the reaction conditions and no competing carboxylation was noted, which offers interesting possibilities for further derivatization. Interestingly, the procedure was also amenable to the production of 2-naphthalen-2-ylacetic acid **11o** in good yield (81%).

In an effort to further highlight the efficiency and attractiveness of our procedure, we next briefly studied its extension to the preparation of heteroarylacetic acids, useful building blocks in medicinal chemistry and agrochemistry (Figure 4). To our delight, benzofuran (**15a**), benzothiophene (**15b**) and indole (**15c**) derivatives could be obtained in fair to good yields from the corresponding bromides. As for pyridin-3-ylacetic acid **15d**, it was also formed by carboxylation of the corresponding bromide, but in lower yield due to the poor stability of the starting material combined with a less efficient reaction and a much more tedious purification.

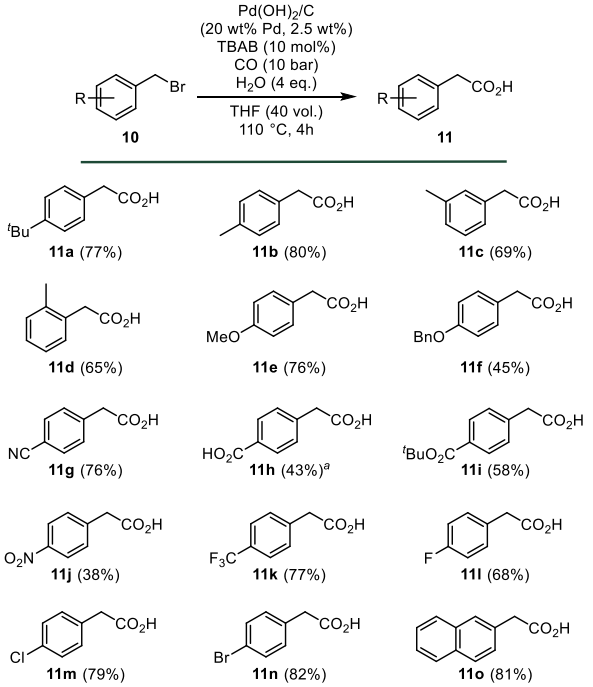


Figure 3. Scope and limitations of the $Pd(OH)_2/C$-catalyzed carboxylation of benzylic bromides. [a] *from ethyl 4-(bromomethyl)benzoate.*

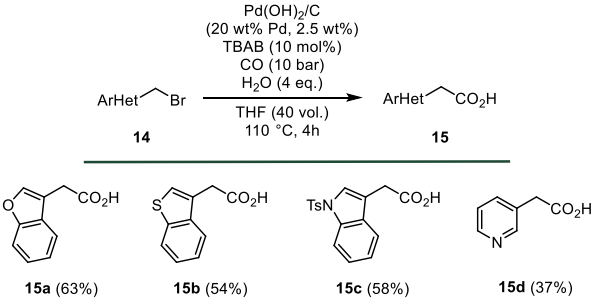


Figure 4. $Pd(OH)_2/C$-catalyzed carboxylation of heterobenzylic bromides.

$Pd(OH)_2/C$-catalyzed carboxylation of benzylic bromides on a multigram scale. In a further effort to demonstrate the synthetic potential of our procedure, a scale up of the carboxylation of *p*-bromo-benzyl bromide **10n** to *p*-bromo-phenylacetic acid **11n** was next explored (Figure 5). A 1 L autoclave was therefore charged with 20 grams of *p*-bromo-benzyl bromide followed by TBAB, water and $Pd(OH)_2/C$ in 800 mL of THF (industrial grade: KF $\leq$ 0.1%). The resulting suspension was purged with carbon monoxide (3 bar) and then heated to 110 °C before

pressurizing with 10 bar of carbon monoxide. The reaction mixture was stirred at 110 °C under 10 bar of carbon monoxide for 6 hours: in-process control (LCAP) revealed the formation of 71% of the targeted product **11n**, 10% of starting material and 11% of the reduced product. Shorter reaction times led to lower conversions and a longer one or the use of additional catalyst did not improve conversion and selectivity. After cooling to 20-25 °C, the mixture was filtered through filter cloth to provide a clear solution which was fully concentrated under atmospheric pressure before adding a 30% aqueous solution of sodium hydroxide, water and dichloromethane. The aqueous layer was next treated with charcoal before adding 34% hydrochloric acid until pH 1-2 and stirring the resulting white slurry at 20-25 °C for 1 hour. The mixture was then held at 0-5 °C for 1 hour, and the solid was collected by filtration. The cake was washed twice with cold water and the solid was oven-dried overnight (40 °C) to afford 10.8 grams of the desired *p*-bromo-phenylacetic acid **11n** (60% yield, 99.3% LCAP).

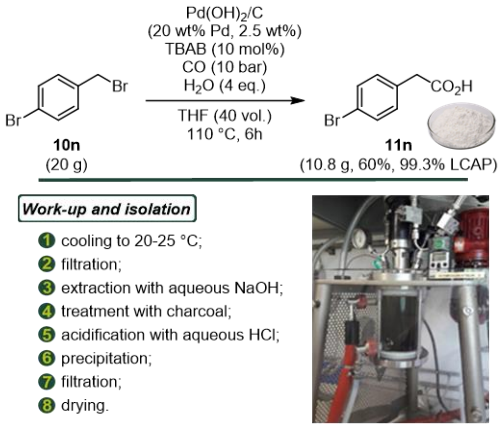
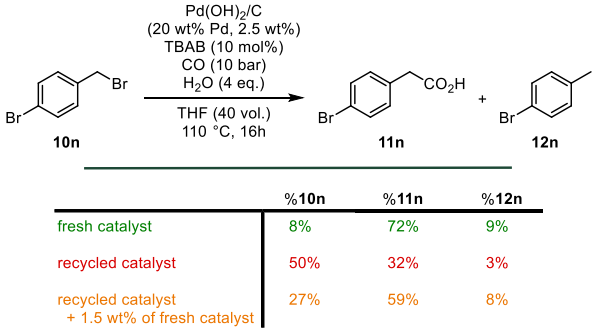


Figure 5. $Pd(OH)_2/C$-catalyzed synthesis of *p*-bromo-phenylacetic acid on a multigram scale.

Heterogeneous nature of the catalyst and catalyst recycling. On an industrial setting, and especially for large scale applications, the nature of the catalyst (*i.e.* heterogeneous *vs*

homogeneous) and its recycling are of crucial importance. Indeed, a totally heterogeneous catalyst with limited leaching ensures low levels of residual palladium into the final product together with facilitating its recycling. We therefore first decided to address the nature of the catalyst and to perform leaching studies: ICP analysis of the crude filtrate prior to any extraction or treatment gratifyingly revealed a really low level of palladium (0.9 ppm) in solution, therefore highlighting the heterogeneous nature of our system.

Our catalytic system being heterogeneous, we could therefore next address its potential recyclability, an important point even if our procedure involves a low catalyst loading. A large scale carboxylation of **10n** was therefore set up and the catalyst that could be recovered after the filtration step was reused for another carboxylation: as demonstrated by the percentage of starting material **10n**, carboxylated and reduced products **11n** and **12n**, whose yields were evaluated by HPLC analysis of the crude reaction mixture, shown in Figure 6, this recycled catalyst was shown to be much less efficient since lower conversion and yield were obtained under otherwise identical conditions. In an attempt to solve this problem, a spiking strategy that is commonly utilized for large scale metal-catalyzed reactions, involving the addition of a minimum of the fresh catalyst to the recycled one was envisioned. This turned out to be rather fruitful since a comparable catalytic activity could be restored, at the expense of the conversion however.



	%10n	%11n	%12n
fresh catalyst	8%	72%	9%
recycled catalyst	50%	32%	3%
recycled catalyst + 1.5 wt% of fresh catalyst	27%	59%	8%

Figure 6. Catalyst recycling.

$Pd(OH)_2$/C-catalyzed carboxylation of benzylic bromides with *ex situ*-generated carbon monoxide in a two-chamber reactor. Having demonstrated the efficiency, the applicability and the scale up of our process for the carboxylation of benzylic bromides with carbon monoxide relying on the use of a heterogeneous and recyclable catalyst, we next moved to a brief study of its extension to the use of precursors of carbon monoxide. Certain academic and industrial laboratories being either not equipped to handle carbon monoxide or reluctant to use it, the use of stable precursors of this reagent indeed provides an interesting alternative, notably for small scale reactions. Skrydstrup's two-chamber reactor COware,[20] in which carbon monoxide is *ex situ*-generated in one chamber before reacting in the second one, having proved its efficiency for such processes, we therefore tested its use for our carboxylation. Among all stable precursors of carbon monoxide reported to date, a combination of formic acid and sulfuric acid[21] – the later dehydrating the former (Morgan reaction)[22] at elevated temperatures – was selected, these two reagents being cheap and readily available.

To test this alternative carboxylation procedure, the CO-generation chamber of a 20 mL two-chamber COware reactor (Figure 7, chamber A) was charged with 10 equiv. of sulphuric acid while

the carboxylation chamber (Figure 7, chamber B) was charged with *p-tert*-butyl-benzyl bromide **10a**, 20 wt% of palladium hydroxide on carbon (20 wt% Pd), 10 mol% of tetrabutylammonium bromide and water (4 equiv.) in THF. The COware reactor was tightly closed, heated at 80 °C and formic acid (10 equiv.) was then added dropwise in the CO-generation chamber. After 24 hours at 80 °C – this temperature being selected to stay within the pressure limit of the two-chamber reactor, – a simple filtration followed by an acid-base extraction provided the desired arylacetic acid **11a** in 54% yield, a yield that was not further optimized but demonstrated that the use of gaseous carbon monoxide is not strictly needed for our carboxylation. As a note, the amount of Pearlman's catalyst as well as the reaction time had to be increased in this case to ensure a full conversion of the starting material.

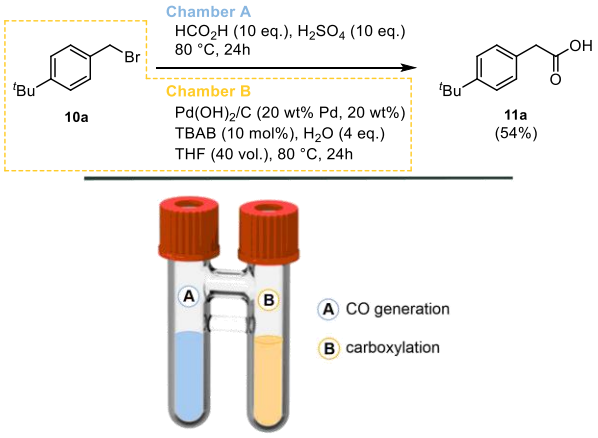
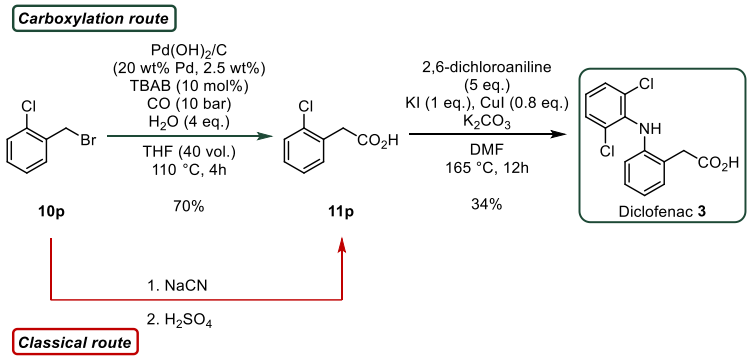


Figure 7. $Pd(OH)_2/C$-catalyzed carboxylation of *p-tert*-butyl-benzyl bromide with *ex situ*-generated carbon monoxide in a two-chamber reactor.

Application to the synthesis of diclofenac. In a final attempt to highlight the synthetic potential of our carboxylation, notably in medicinal and process chemistry, we envisioned its use for the synthesis of an API. Diclofenac **3**, commercialized under various trade names such as

Voltaren™, Cataflam™, or Pennsaid™, was selected as the target due to its importance as a non-steroidal anti-inflammatory drug which has been among the best-selling anti-inflammatory drugs for more than a decade and due to the number of processes reported and patented for its synthesis.[23] It was first patented in 1965 by Ciba-Geigy and came into medical use in 1988.[24]

Among all the syntheses reported and/or patented, the ones relying on an Ullmann coupling are especially appealing in terms of number of steps and availability/cost of the starting materials. This was actually already featured in one of Ciba-Geigy's original routes which involved a key Ullmann coupling between 2,6-dichloroaniline and *o*-chloro-benzoic acid.[23a] Starting from an *o*-halo-phenylacetic acid in place of the corresponding benzoic acid resulting in more straightforward syntheses, several processes have been developed based on this strategy, using *o*-iodo-phenylacetic,[25] *o*-bromo-phenylacetic,[26] or *o*-chloro-phenylacetic[10,27] acids, the latter being more appealing in terms of cost, although its amination being challenging. While its classical preparation from *o*-chloro-benzyl bromide or chloride rely on a nucleophilic substitution with a cyanide followed by hydrolysis (Scheme 2, bottom), it could be more conveniently prepared by a direct carboxylation with carbon monoxide (Scheme 2, top).[10] We therefore envisioned testing the efficiency of our catalytic system for this step: with this goal in mind, *o*-chloro-benzyl bromide **10p** was thus reacted under our optimized conditions, providing *o*-chloro-phenylacetic acid **11p** in 70% after filtration and a simple acid-base wash. A further coupling with 2,6-dichloroaniline under previously reported conditions[10] then afforded diclofenac **3** in two steps from commercially available starting materials.



Scheme 2. $Pd(OH)_2$/C-catalyzed carboxylation of benzylic bromides applied to the synthesis of diclofenac.

3. CONCLUSION

In conclusion, we have developed a simple, efficient and broadly applicable system for the carboxylation of benzylic bromides. Upon simple reaction with carbon monoxide and water in the presence of only 2.5 wt% of Pearlman's catalyst and 10 mol% of TBAB in THF at 110 °C for 4 hours, a range of benzylic bromides can be smoothly converted to the corresponding arylacetic acids in good to excellent yields. The reaction was found to be rather general, scalable and both its extension to *ex situ*-generated carbon monoxide and its application to the synthesis of the non-steroidal anti-inflammatory drug diclofenac highlight its synthetic potential. Attractive features of this procedure include the low cost of the palladium catalyst, its easy removal by simple filtration, the operational simplicity of the process and its generality and broad substrate scope. It should facilitate the synthesis of arylacetic acids and could contribute to the development of shorter and more efficient industrial processes.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried glassware unless otherwise stated.

All solvents were reagent grade. Tetrahydrofuran was freshly distilled from sodium/benzophenone under argon prior to use (for small scale reactions – for the large scale reaction, industrial grade THF (KF $\leq$ 0.1%) was used without purification). *N*,*N*-Dimethylformamide (99.8% purity, Extra Dry over Molecular Sieves, Acroseal®) was purchased from ACROS Organics and degassed by three cycles of "freeze-pump-thaw" using argon as inert gas when required.

Palladium hydroxide on carbon (20 wt% Pd, moisture *ca* 60%) was purchased from ACROS Organics and used as supplied. Tetrabutylammonium bromide (98% purity) was purchased from Combi-Blocks and used as supplied. Copper(I) iodide (99,999% purity) used for copper-mediated coupling reactions was purchased from ACROS Organics and used as supplied. Carbon monoxide (N47, 99.997%+ purity) was purchased from Air Liquide and used as supplied. Deuterium oxide (99.9% D) was purchased from Eurisotop and used as supplied. Sulfuric acid (96%, VLSI Selectipur®) and formic acid (99%+ purity) were respectively purchased from BASF and ACROS Organics and used as supplied. All other reagents were used as supplied.

Carboxylation reactions were performed using a HEL ltd. CAT 7 autoclave (https://www.helgroup.com) equipped with B19 PTFE-capped 10 mL glass vials and linked to a CO cylinder. The 20 mL two-chamber COware reactor was purchased from Sigma-Aldrich.

Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kiesegel 60F_{254} plates. Flash chromatography was performed with silica gel 60 (particle size 35-70 µm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Proton NMR spectra were recorded using an internal deuterium lock at ambient temperature on Bruker 300 MHz, Varian 400 MHz and JEOL 400 MHz spectrometers. Internal reference of δ_H 7.26 was used for $CDCl_3$, and δ_H 2.05 was used for acetone-d_6. Carbon-13 NMR spectra were recorded at 100 MHz using $CDCl_3$ (δ_C 77.16) or acetone-d_6 (δ_C 29.84) as internal reference. ^{19}F NMR spectra were recorded at 376 MHz.

Carboxylation with Deuterated Water. *Synthesis and Isolation of p-tert-Butyl-toluene* ***12a$_D$*** *and p-tert-Butyl-benzyl Alcohol* ***13a***. Six glass vials containing a PTFE-coated magnetic stirrer were each charged with *p-tert*-butyl-benzyl bromide **10a** (115 mg, 0.52 mmol), palladium hydroxide on carbon 20 wt% (3 mg, 2.5 wt%) and tetrabutylammonium bromide (19 mg, 0.06 mmol). Tetrahydrofuran (2.3 mL, 20 vol.) and deuterium oxide (38 µL, 2.08 mmol) were then added, the vials were sealed with a PTFE cap and placed in the autoclave. The system was first purged with 5 bar of CO, then pressurized with 10 bar of CO and stirred at 110 °C for 12 hours. The autoclave was cooled down to room temperature and then gently depressurized. The content of the six vials was combined and filtered over a short pad of Celite®, which was thoroughly washed with ethyl acetate (*ca* 20 mL). The volatiles were removed under reduced pressure. The crude residue was dissolved in a 1M aqueous solution of sodium hydroxide (10 mL) and washed with pentane (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel

(pentane to pentane/diethyl ether: 75/25) to afford the reduced product **12a$_D$** (64%D, 24 mg, 0.16 mmol, 5%) as a colorless liquid and the hydrolyzed compound **13a** (15 mg, 0.09 mmol, 3%) as a colorless liquid. These compounds have been previously reported.[28]

Carboxylation of Benzylic Bromides. *General Procedure.* Three glass vials containing a PTFE-coated magnetic stirrer were each charged with the desired benzylic bromide **10** (57 mg, 1.0 equiv.), palladium hydroxide on carbon 20 wt% (1.5 mg, 2.5 wt%) and tetrabutylammonium bromide (0.1 equiv.). Tetrahydrofuran (2.3 mL, 40 vol.) and distilled water (4 equiv.) were then added, the vials were sealed with a PTFE cap and placed in the autoclave. The system was first purged with 5 bar of CO, then pressurized with 10 bar of CO and stirred at 110 °C for 4 hours. The autoclave was cooled down to room temperature and then gently depressurized. The content of the three vials was combined and filtered over a short pad of Celite®, which was thoroughly washed with ethyl acetate (*ca* 10 mL). The volatiles were removed under reduced pressure. The crude residue was dissolved in a 1M aqueous solution of sodium hydroxide (5 mL) and washed with pentane (3 x 5 mL). The aqueous layer was then acidified to pH 1-2 with a 10% aqueous solution of hydrochloric acid and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired carboxylic acid **11** as a solid. The product thus obtained did not require further purification.

*p-tert-Butyl-phenylacetic Acid **11a***. Yield: 77% (113 mg, 0.59 mmol). White solid. This compound has been previously reported.[7a]

p-Tolylacetic Acid ***11b***. Yield: 80% (90 mg, 0.60 mmol). White solid. This compound has been previously reported.[29]

m-Tolylacetic Acid ***11c***. Yield: 69% (81 mg, 0.54 mmol). White solid. This compound has been previously reported.[29]

o-Tolylacetic Acid ***11d***. Yield: 65% (91 mg, 0.61 mmol). Off-white solid. This compound has been previously reported.[30]

p-Methoxy-phenylacetic Acid ***11e***. Yield: 76% (108 mg, 0.65 mmol). White solid. This compound has been previously reported.[7a]

p-Benzyloxy-phenylacetic Acid ***11f***. Yield: 45% (92 mg, 0.38 mmol). White solid. This compound has been previously reported.[31]

p-Cyano-phenylacetic Acid ***11g***. Yield: 76% (106 mg, 0.66 mmol). White solid. This compound has been previously reported.[32]

p-Carboxy-phenylacetic Acid ***11h***. Prepared according to the general procedure starting from ethyl *p*-(bromomethyl)benzoate **10h**. Yield: 43% (51 mg, 0.28 mmol). White solid. This compound has been previously reported.[33]

p-tert-Butoxycarbonyl-phenylacetic Acid ***11i***. Yield: 58% (86 mg, 0.36 mmol). White solid. This compound has been previously reported.[34]

p-Nitro-phenylacetic Acid ***11j***. Yield: 38% (55 mg, 0.30 mmol). Yellow solid. This compound has been previously reported.[35]

p-Trifluoromethyl-phenylacetic Acid ***11k***. Yield: 77% (147 mg, 0.62 mmol). Off-white solid. This compound has been previously reported.[7a]

p-Fluoro-phenylacetic Acid ***11l****.* Yield: 68% (96 mg, 0.62 mmol). White solid. This compound has been previously reported.[7a]

p-Chloro-phenylacetic Acid ***11m****.* Yield: 79% (113 mg, 0.66 mmol). White solid. This compound has been previously reported.[29]

p-Bromo-phenylacetic Acid ***11n****.* Yield: 82% (121 mg, 0.56 mmol). White solid. This compound has been previously reported.[29]

Naphthalen-2-ylacetic Acid ***11o****.* Yield: 81% (117 mg, 0.63 mmol). White solid. This compound has been previously reported.[7a]

o-Chloro-phenylacetic Acid ***11p***. Yield: 70% (101 mg, 0.59 mmol). White solid. This compound has been previously reported.[7a]

Benzofuran-3-ylacetic Acid ***15a***. Yield: 63% (90 mg, 0.51 mmol). White solid. This compound has been previously reported.[36]

Benzo[b]thiophen-3-ylacetic Acid ***15b****.* Yield: 54% (78 mg, 0.41 mmol). White solid. This compound has been previously reported.[37]

N-Tosyl-indol-3-ylacetic Acid ***15c****.* Yield: 58% (93 mg, 0.28 mmol). Brownish solid. This compound has been previously reported.[38]

Pyridin-3-ylacetic Acid ***15d****.* This compound was prepared starting from 3-(bromomethyl)pyridine hydrobromide. The hydrobromide (253 mg, 1.0 mmol) was dissolved in a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and the resulting free base was extracted with diethyl ether (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 3-(bromomethyl)pyridine

14d which was used quickly following the general carboxylation procedure. Instead of an acid-base wash, trituration of the crude residue in chloroform (5 mL) and filtration delivered the desired acid **15d**. Yield: 37% (46 mg, 0.34 mmol). White solid. This compound has been previously reported.[39]

Multigram Scale Procedure. *Carboxylation of p-Bromo-benzyl Bromide **10n**.* A 1L autoclave was charged with *p*-bromo-benzyl bromide **10n** (20 g, 80.0 mmol), tetrabutylammonium bromide (2.58 g, 8.0 mmol), distilled water (5.8 mL, 320 mmol), palladium hydroxide on carbon 20 wt% (0.5 g, 2.5 wt%) and tetrahydrofuran (industrial grade: KF $\leq$ 0.1%, 800 mL). The resulting suspension was purged with 3 bar of CO and heated to 110 °C before being pressurized with 10 bar of CO. The reaction mixture was stirred at 110 °C under 10 bar of CO for 6 hours (In-process control (LCAP): 71% targeted product **11n**, 10% starting material **10n**, 11% reduced product **12n**). The resulting mixture was cooled down to room temperature and filtered through filter cloth to provide a clear solution which was concentrated under atmospheric pressure. A 30% aqueous solution of sodium hydroxyde (80 mL), water (100 mL) and dichloromethane (100 mL) were then added to the residue and the organic and aqueous phases were separated. The aqueous layer was treated with charcoal and a 34% aqueous solution of hydrochloric acid was added to reach pH 1-2. The resulting white slurry was then stirred at 20-25 °C for 1 hour and held at 0-5 °C for an additional hour before being collected as a solid by filtration. The cake was washed with cold water (2 x 10 mL) and the resulting solid was oven-dried overnight (40 °C) to yield *p*-bromo-phenylacetic acid **11n** as a white solid (10.8 g, 50.2 mmol, 60%, 99.3% LCAP). This compound has been previously reported.[29]

COware Two-Chamber Reactor Procedure. *Carboxylation of p-tert-Butyl-benzyl Bromide **10a**. p-tert*-Butyl-benzyl bromide **10a** (57 mg, 0.26 mmol), palladium hydroxide on carbon 20 wt% (12 mg, 20 wt%), tetrabutylammonium bromide (10 mg, 0.03 mmol), distilled water (19 μL, 1.04 mmol) and tetrahydrofuran (2.3 mL, 40 vol.) were charged in the carboxylation chamber of a 20 mL two-chamber COware reactor. Sulfuric acid (140 μL, 2.6 mmol) was added in the CO-generation chamber. The COware reactor was tightly closed, heated at 80 °C and formic acid (100 μL, 2.6 mmol) was then added dropwise in the CO-generation chamber. The mixture was stirred at 80 °C for 24 hours. The two-chamber reactor was cooled down to room temperature and then gently depressurized. The content of the carboxylation chamber was filtered over a short pad of Celite®, which was thoroughly washed with ethyl acetate (*ca* 5 mL). The volatiles were removed under reduced pressure. The crude residue was dissolved in a 1M aqueous solution of sodium hydroxide (5 mL) and washed with pentane (3 x 5 mL). The aqueous layer was then acidified to pH 1-2 with a 10% aqueous solution of hydrochloric acid and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield *p-tert*-butyl-phenylacetic acid **11a** as a white solid (27 mg, 0.14 mmol, 54%). This compound has been previously reported.[7a]

Diclofenac Synthesis. *Ullmann Coupling on p-Chloro-phenylacetic Acid **11m**.* A 50 mL pressure tube fitted with a rubber septum was charged with *p*-chloro-phenylacetic acid **11m** (512 mg, 3.0 mmol), 2,6-dichloroaniline (2.43 g, 15.0 mmol), copper(I) iodide (457 mg, 2.4 mmol), potassium iodide (498 mg, 3.0 mmol) and potassium carbonate (829 mg, 6.0 mmol). The pressure tube was evacuated under high vacuum, backfilled with argon and then degassed *N*,*N*-dimethylformamide (6 mL) was added. The pressure tube was then sealed with a Teflon-coated

screw cap and stirred 12 hours at 165 °C. The resulting dark mixture was cooled down to room temperature and transferred into a 250 mL round bottom flask. Ethyl acetate (120 mL), water (60 mL), concentrated hydrochloric acid (4.0 mL) as well as charcoal (12 g) and Celite® (12 g) were added and the resulting slurry was vigorously stirred for 1 hour. The mixture was filtered, the biphasic filtrate was separated, and the organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 80/20 to 60/40) to give the desired acid **3** (293 mg, 0.99 mmol, 34%) as a white solid. This compound has been previously reported.[10,25c]

ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra (PDF) and Primary NMR data files (ZIP). This material is available free of charge on the ACS Publication Website.

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Notes

The authors declare no competing financial interest.

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