Renewable Solvents for Palladium-Catalyzed Carbonylation Reactions

Aya Ismael, Ashot Gevorgyan, Troels Skrydstrup, and Annette Bayer*

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ABSTRACT: Solvents constitute the largest component for many chemical processes and substitution of nonrenewable solvents is a longstanding goal for green chemistry. Here, we show that Pd-catalyzed carbonylative couplings, such as carbonylative cross-couplings, aminocarbonylations, and alkoxycarbonylations, can be successfully realized using renewable solvents. The present research covers not only well-established renewable solvents, such as 2-methyltetrahydrofuran (2MeTHF), limonene, and dimethyl carbonate, but also recently introduced biomass-derived 1,1-diethoxyethane, isosorbide dimethyl ether, eucalyptol, rose oxide, γ-terpinene, and α-pinene. The carbonylative coupling of boronic acids and aryl bromides works well in limonene. Aminocarbonylation gave excellent results in dimethyl carbonate, α-pinene, and limonene, while alkoxycarbonylation was successful in 2MeTHF, α-pinene, γ-terpinene, and dimethyl carbonate. The developed methods based on renewable solvents can be used for the synthesis of commercial drug Trimetozine and an analogue of Itopride.

KEYWORDS: renewable solvents, carbonylative C−C coupling, aminocarbonylation, alkoxycarbonylation, palladium catalysis, carbon monoxide

■ INTRODUCTION

According to the development plan of the United Nations General Assembly "*Transforming Our World: The 2030 Agenda for Sustainable Development*" initiated in 2015, considerable efforts are needed over the coming decade to build a better and more sustainable future.[1] The realization of most of the aspects of "*The 2030 Agenda for Sustainable Development*" can be directly conditioned by sustainable innovations in chemical research.

Today, most of the industrial processes and particularly the pharmaceutical industry are largely based on the application of nonrenewable solvents, which usually constitute over 80% of materials needed for the production of the final ingredients.[2] As a result, yearly manufacture of nonrenewable and hazardous common organic solvents exceeds 20 million metric tons.[2d] A recent survey on the solvents used in the pharmaceutical industry for the period 1997−2012 revealed that the top 10 most frequently used solvents are dichloromethane, hexane, diisopropyl ether, 1,2-dimethoxyethane, 1,4-dioxane, 1,2-dichloroethane, diethyl ether, chloroform, diglyme, and chlorobenzene.[3] This unsustainable practice can be addressed by the development and popularization of renewable and safe solvent candidates.

Liquids or low melting chemicals available from the valorization of biomass[4,5] as well as chemicals derived from the reduction of CO_2[6,7] have enormous potential to replace the common nonrenewable solvents utilized in organic synthesis.[3] The most frequently used solvents available from biomass are polar protic ethanol, glycerol and its derivatives, and choline chloride-based deep eutectic solvents, polar aprotic 2-methyltetrahydrofuran (2MeTHF), cyrene and γ-valerolactone (GVL), as well as nonpolar limonene and p-cymene (Figure 1).[4,5] Moreover, CO_2-derived carbonates and ethers such as dimethoxymethane (methylal) have attracted attention as solvents (Figure 1).[6,7] Recently, we have shown that biomass-derived solvents such as nonpolar ethers (1,1-diethoxyethane (acetal), dimethyl isosorbide, eucalyptol, rose oxide) and terpenes (γ-terpinene and α-pinene) can be successfully used in Cu-catalyzed carboxylation reactions (Figure 1).[51]

A complete life cycle assessment (LCA) of the latter solvents is not available, but most of them are significantly less toxic compared to common organic solvents.[8] Low toxicity is particularly inherent to naturally occurring dimethyl isosorbide, GVL and eucalyptol, ethanol-derived acetal, as well as CO_2-derived diethyl carbonate (DEC), dimethyl carbonate (DMC), and methylal. Among others, these solvents are used in large quantities in the pharmaceutical and food industries as additives, antiseptics, and flavoring agents.[9] There is no need to continue increasing the consumption of nonrenewable solvents for processes where renewable solvents provide comparable outcome.

Renewable solvents have proven to be suitable for a variety of transformations including classical condensation reactions and transition-metal (TM)-catalyzed cross-couplings.[4−6] However, the use of renewable solvents as reaction media for carbonylative couplings with CO remain largely unex-
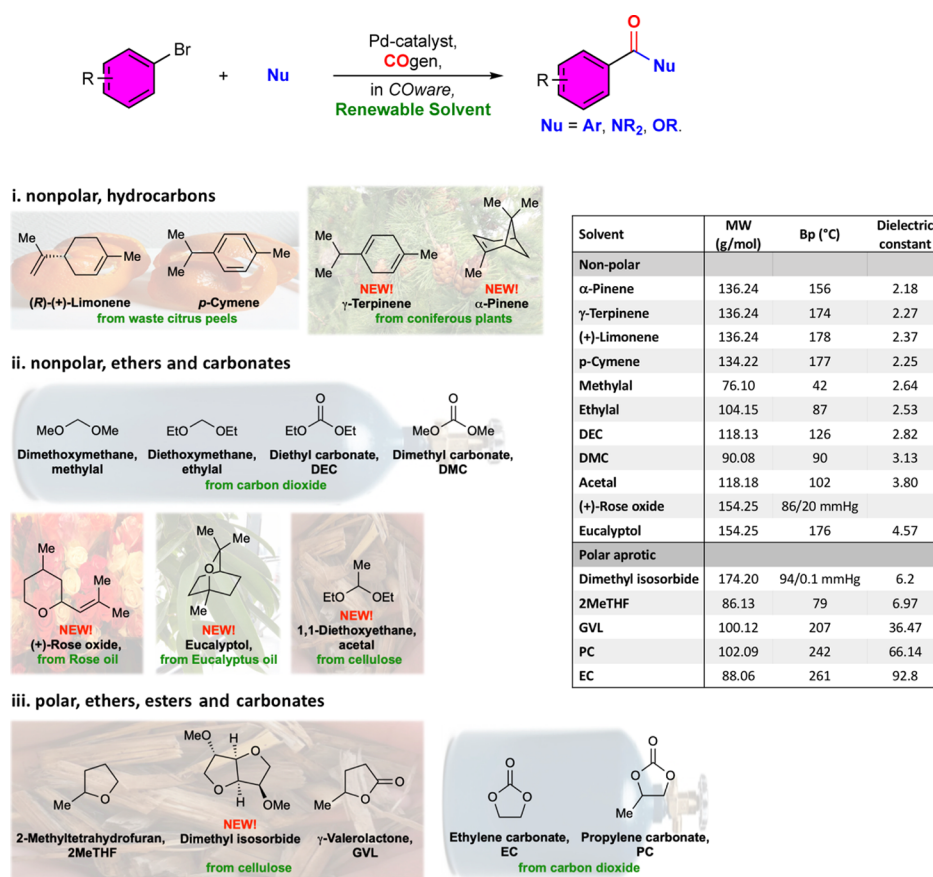
Figure 1. Overview of the present work and renewable solvents used in the work (pictures taken by A.G.).

plored.[10,11] The fact that the Pd-catalyzed carbonylations have found numerous applications in modern drug discovery and isotopic labeling of pharmaceuticals[10d,e,g] makes the development of renewable methodologies for carbonylations a task of great significance. This work describes the use of newly introduced biomass-derived solvents (acetal, dimethyl isosorbide, γ-terpinene, α-pinene, eucalyptol, and rose oxide, Figure 1) and previously studied renewable solvents (2MeTHF, GVL, limonene, p-cymene, DMC, DEC, ethylene carbonate (EC), propylene carbonate (PC), methylal and diethoxymethane (ethylal), Figure 1) for Pd-catalyzed carbonylations.

RESULTS AND DISCUSSION

A range of renewable solvents were studied for carbonylative couplings of aryl bromides with arylboronic acids,[12] amines (aminocarbonylation),[13] and alcohols (alkoxycarbonylation) (Figure 1).[14] We decided to focus on Pd-based catalytic systems that have proven to be versatile catalysts for carbonylative couplings.[11k,12–14] For safety reasons, the reactions were conducted in two chamber reactors (COware) developed in the group of Skrydstrup using stoichiometric quantities of CO generated *ex situ* from COgen (9-methyl-9H-fluorene-9-carbonyl chloride).[10e] The solvent's polarity was approximated as nonpolar and polar based on their dielectric constant; a solvent was classified as polar if the dielectric constant was over 5 (Figure 1, Table S1).

Carbonylative C–C Couplings of Aryl Bromides and Arylboronic Acids. As a starting point, we analyzed the carbonylative coupling of 3-bromoanisole with m-tolylboronic

acid (Chart 1). We focused on the catalytic system based on Pd(acac)$_2$ as catalyst precursor and di(1-adamantyl)-n-

Chart 1. Screening of Renewable Solvents for Carbonylative Coupling of m-Tolylboronic Acid and 3-Bromoanisole
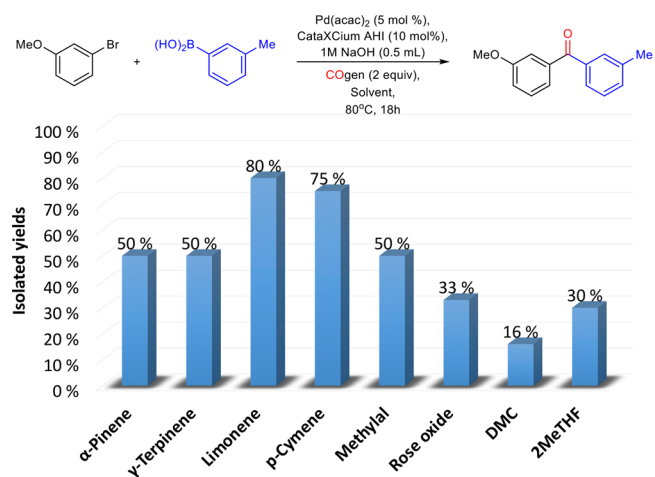
butylphosphine hydroiodide (cataCXium AHI) as ligand, developed in the group of Skrydstrup.[12g] The original protocol relied on cyclic diethanolamine esters of boronic acids (DABO boronates) or aryl trihydroxyborates as successful starting materials and used toluene/H$_2$O (10:1) or toluene as solvent.[12g] We initiated our work by developing a simplified protocol where the aryl trihydroxyborates were generated *in situ* from simple boronic acids by addition of 1 M aqueous

Scheme 1. Scope of Carbonylative Coupling of Boronic Acids and Aryl Bromides Using the Sustainable Solvent Limonene
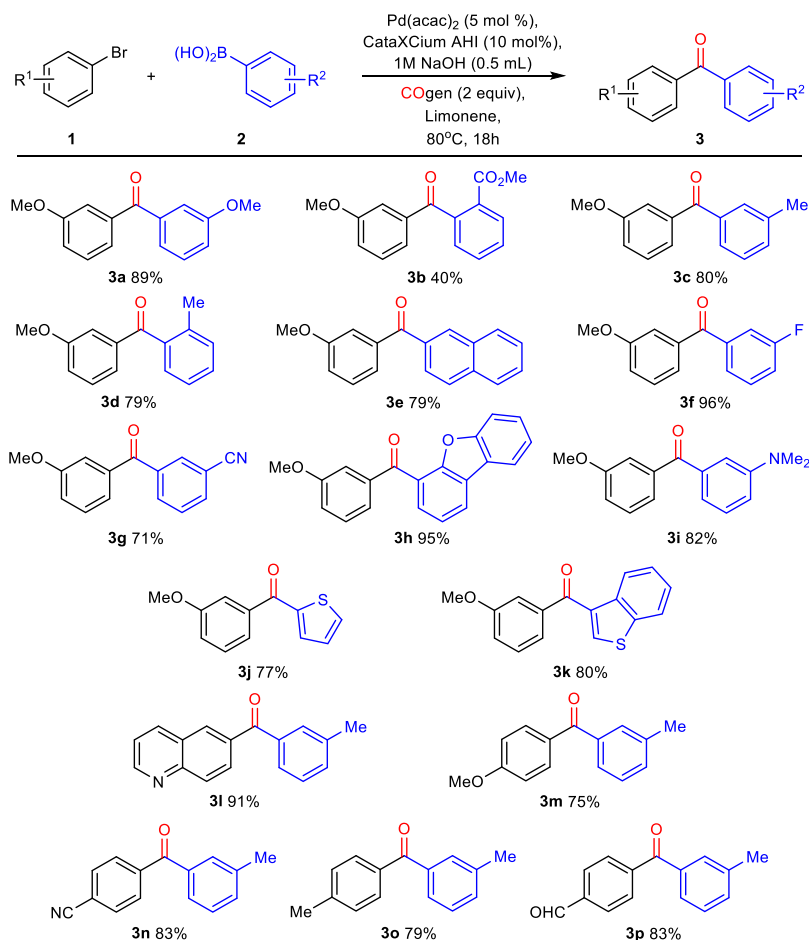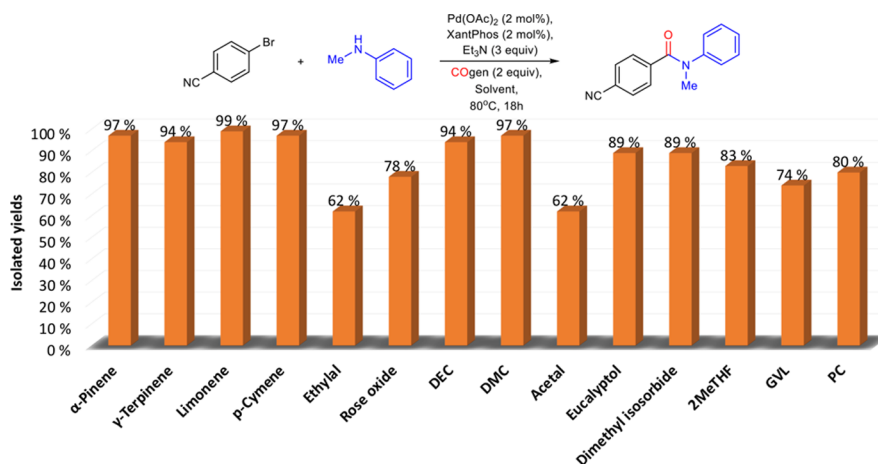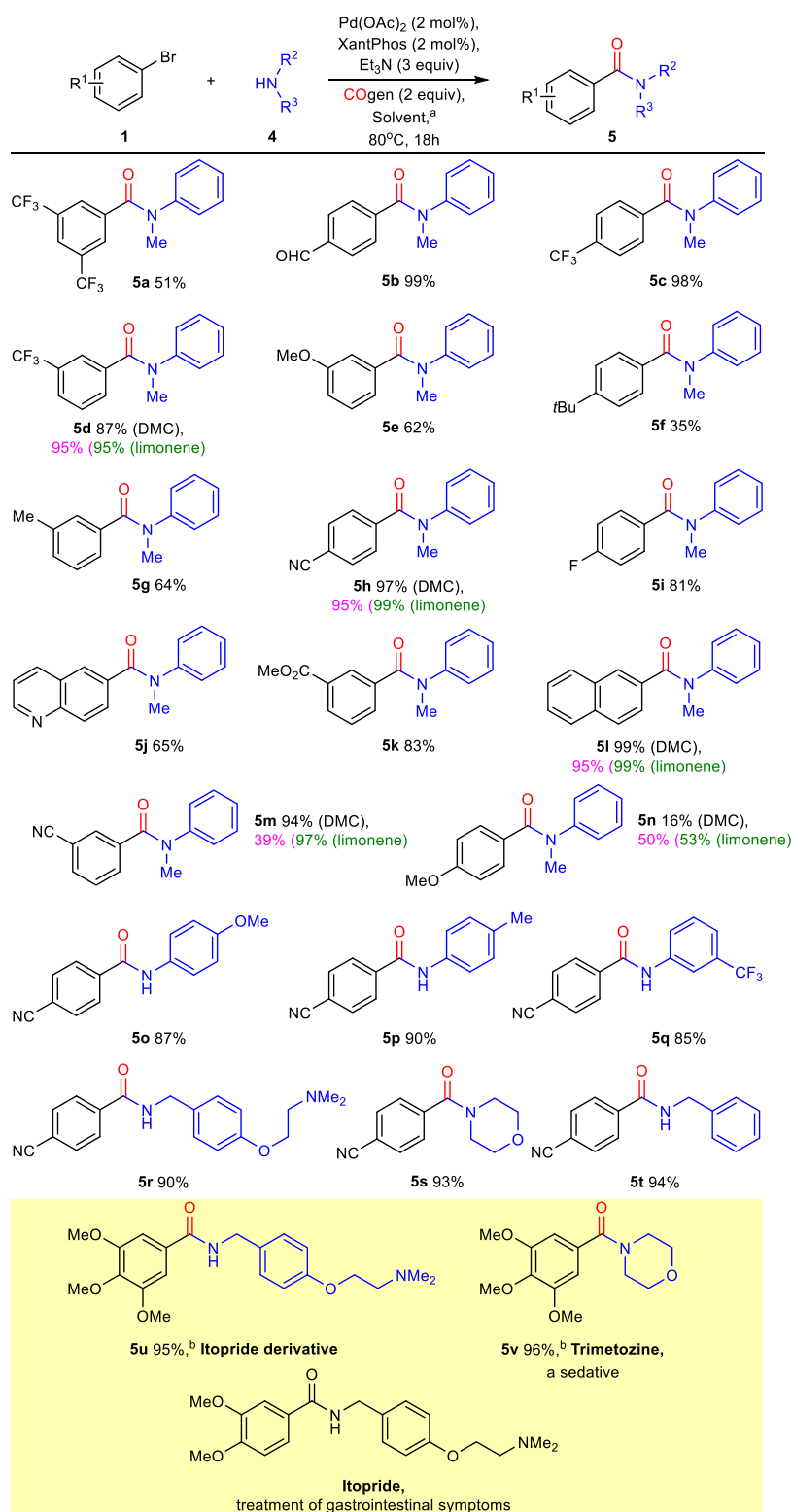

Chart 2. Screening of Renewable Solvents for Aminocarbonylation with Resulting Isolated Yields

NaOH, thus preventing the external, up-front preparation of the organoboronate (see Table S1, entry 3).

Using the modified protocol, we investigated the efficiency of various renewable solvents in the Pd-catalyzed carbonylative coupling of *m*-tolylboronic acid and 3-bromoanisole (Chart 1, see also Table S1 for a correlation of solvent polarity and yields). It has to be noted that the final reaction media contained approximately 15% (v/v) of water in all cases because of the addition of aqueous NaOH. Our studies revealed that nonpolar ethers and carbonates (rose oxide,

methylal, DMC) and polar ether 2MeTHF provide the carbonylation product in low to moderate yields (16−50%). In contrast, biomass-derived nonpolar hydrocarbons (limonene, *p*-cymene, *γ*-terpinene, *α*-pinene) gave consistently better yields with *p*-cymene and limonene being the best solvents (75 and 80% isolated yield, respectively), an observation that correlates well with the use of toluene or toluene/water as solvent in previous studies providing the corresponding product in 90% yield.[12g] Although limonene possesses a terminal and an internal double bond, the Heck-

Scheme 2. Scope of Aminocarbonylation of Aryl Bromides[a]

5a 51%
5b 99%
5c 98%

5d 87% (DMC), 95% (95% (limonene)
5e 62%
5f 35%

5g 64%
5h 97% (DMC), 95% (99% (limonene)
5i 81%

5j 65%
5k 83%
5l 99% (DMC), 95% (99% (limonene)

5m 94% (DMC), 39% (97% (limonene)
5n 16% (DMC), 50% (53% (limonene)

5o 87%
5p 90%
5q 85%

5r 90%
5s 93%
5t 94%

5u 95%,[b] **Itopride derivative**

5v 96%,[b] **Trimetozine,** a sedative

Itopride, treatment of gastrointestinal symptoms

[a]Unless otherwise mentioned, the reaction was performed in DMC. [b]XantPhos Pd G3 was used instead of Pd(OAc)$_2$/XantPhos.

type arylation of the solvent was not observed under the reaction conditions. Neither were related side products noted for reactions in rose oxide, γ-terpinene, and α-pinene.

We proceeded to analyze the generality of the Pd-catalyzed carbonylative couplings in limonene as solvent (Scheme 1). Examination of a variety of aromatic boronic acids and aryl

bromides indicated a good substrate scope. The yields varied from 71 to 95% for electron-rich (**3a, 3c, 3d, 3e, 3h, 3i**), electron-deficient aryl (**3f, 3g**), and heterocyclic boronic acids (**3j, 3k**). The broad applicability of boronic acids is particularly interesting as the use of *in situ*-generated aryl trihydroxyborates extended the substrate scope beyond the limitations associated

Chart 3. Screening of Renewable Solvents for Alkoxycarbonylation with Resulting Isolated Yields[a]
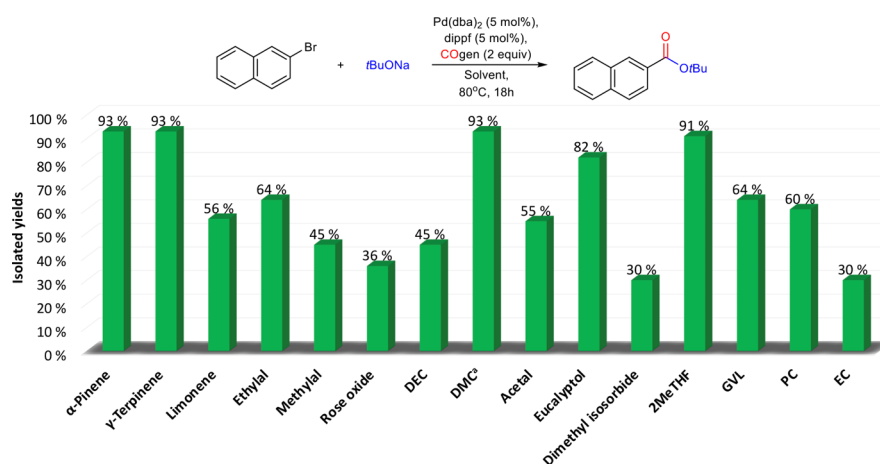
[a] In DMC, methoxycarbonylation was observed.

with isolation of unstable trihydroxyborate salts.[12g] Similarly, both electron-rich (**3m**, 75%; **3o**, 79%) and electron-deficient (**3n**, 83%; **3p**, 83%) aryl bromides as well as heteroaryl bromides (**3l**, 91%) were successful in the carbonylative couplings. We observed a low yield only for 2-methoxycarbonylphenylboronic acid (**3b**, 40%), which may be due to steric hindrance or side reactions such as hydrolysis of the ester. Overall, the observed yields were at the same level as previously reported protocols using toluene as solvent,[12e,g] indicating that limonene is a renewable alternative for carbonylative couplings of boronic acids and aryl bromides.

Aminocarbonylation of Aryl Bromides. Next, we examined the Pd-catalyzed aminocarbonylation reaction of aryl bromides. Here, we focused on the catalytic system developed in the group of Buchwald using Pd(OAc)$_2$ as Pd source, 4,5-bis(diphenylphosphino)-9,9-dimethyl−xanthene (XantPhos) as ligand, and toluene as solvent.[14c] The Pd-catalyst was tested in renewable solvents on the model reaction of N-methylaniline with 4-bromobenzonitrile (Chart 2).

Our studies demonstrated that for this aminocarbonylation, exceptional results can be obtained in most of the renewable solvents (Chart 2). As a general trend, all reactions in nonpolar hydrocarbons provided excellent yield (limonene, 99%; p-cymene, 97%; γ-terpinene, 94%; α-pinene; 97%), in good correlation with previous work performed with toluene as solvent, providing the product in 97% yield.[14c] Excellent yields were also obtained in nonpolar carbonates (DMC, 97%; DEC, 94%). Other solvents such as polar carbonate PC and lactone GVL, and nonpolar and polar ethers (ethylal, acetal, rose oxide, eucalyptol, dimethyl isosorbide, 2MeTHF) were less efficient, with yields ranging between 62 and 89%.
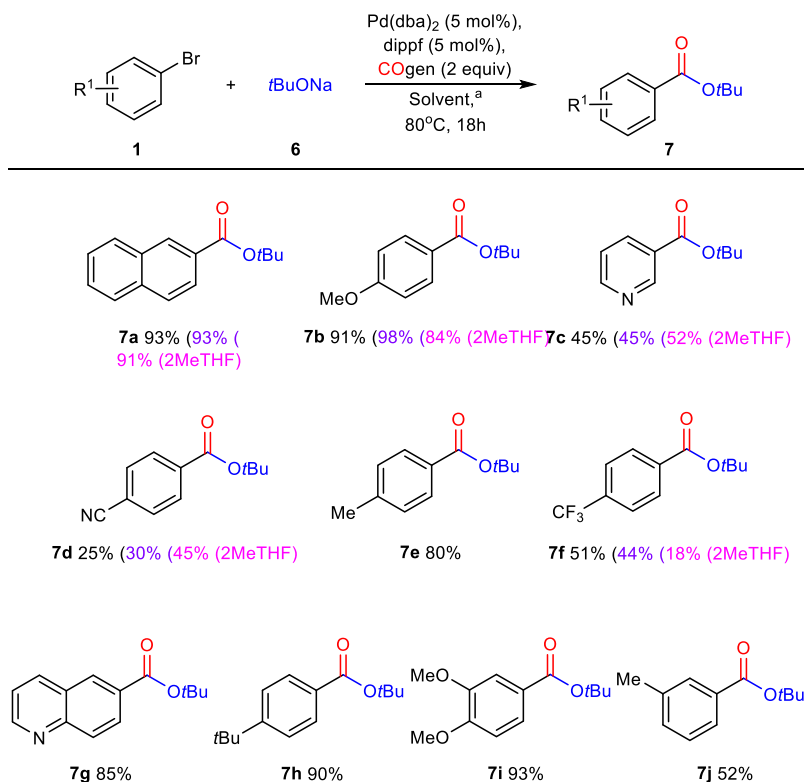
Noteworthily, under the conditions used for aminocarbonylation, we did not observe side reactions such as hydroamination or Mizoroki−Heck coupling for solvents possessing double bonds.

As several renewable solvents provided good yields, we screened the top three best solvents (DMC, α-pinene, limonene) for several aminocarbonylations (Scheme 2). These studies revealed that except for the products **5m** and **5n**, the best solvents DMC, α-pinene, and limonene gave comparable results for several aminocarbonylations (**5d**, **5h**, **5l**). For the product **5m**, α-pinene (39%) turned out far less effective than other solvents, while for the product **5n**, DMC

provided low yield (16%) (Scheme 2). For an extended analysis of the substrate scope, we therefore decided to focus on the use of DMC, as it is considerably less toxic and less expensive than the two other solvents.[15]

Reactions with variously substituted aryl bromides illustrated that many functional groups (CHO, CN, CO$_2$Me) were well tolerated. In general, aryl bromides with electron-withdrawing substituents provided corresponding aminocarbonylation products in good to quantitative yields (**5b**, 99%; **5c**, 98%; **5d**, 87%; **5h**, 97%; **5i**, 81%; **5k**, 83%; **5m** 94%), except for **5a** (51% yield). Electron-rich aryl bromides were less effective, producing the corresponding amides from low to acceptable yields (**5e**, 62%; **5f**, 35%; **5g**, 64%; **5n**, 16%). However, the aminocarbonylation of electron-rich 3,4,5-trimethoxyphenyl bromide, using XantPhos Pd G3 as the catalyst, provided the commercial drug Trimetozine (**5v**, 96% yield, a sedative) and an analogue of Itopride (**5u**, 95% yield, Itopride is used for the treatment of gastrointestinal symptoms) in excellent yields.[13h] The reaction worked well also with fused systems such as naphthalene (**5l**, 99%) and heterocycles (**5j**, 65%) (Scheme 2). Changes in the amine structure were tolerated well and both anilines with electron-donating and -withdrawing substituents, and primary and secondary aliphatic amines were successfully coupled with 4-bromobenzonitrile and CO (Scheme 2, **5o**, 87%; **5p**, 90%; **5q**, 85%; **5r**, 90%; **5s**, 93%; **5t**, 94%). Overall, the observed trends were in agreement with reports of aminocarbonylations performed in nonrenewable solvents.[13,14c] The good yields and substrate scope indicate that renewable solvents such as DMC, α-pinene, and limonene can effectively replace 1,4-dioxane, toluene, and THF frequently used in Pd-catalyzed aminocarbonylation reactions.[10b,13,14c]

Alkoxycarbonylation of Arylbromides. Finally, we analyzed the potential adaptation of renewable solvents for Pd-catalyzed alkoxycarbonylation.[14] For the initial studies, we examined the alkoxycarbonylation of 2-bromonaphthalene with sodium tert-butoxide and CO using the catalytic system based on Pd(dba)$_2$ as catalyst precursor and 1,1′-bis-(diisopropylphosphino)ferrocene (dippf) as ligand first reported by Skrydstrup and co-workers for alkoxycarbonylations in THF (Chart 3).[14f] The screening of renewable solvents showed that excellent results can be achieved also for the Pd-catalyzed alkoxycarbonylations (Chart 3).

Scheme 3. Scope of *tert*-Butoxycarbonylation of Aryl Bromides[a]

7a 93% (93% (γ-terpinene), 91% (2MeTHF)

7b 91% (98% (γ-terpinene), 84% (2MeTHF)

7c 45% (45% (γ-terpinene), 52% (2MeTHF)

7d 25% (30% (γ-terpinene), 45% (2MeTHF)

7e 80%

7f 51% (44% (γ-terpinene), 18% (2MeTHF)

7g 85%

7h 90%

7i 93%

7j 52%

[a]Unless otherwise mentioned, the reaction was performed in α-pinene.

Not surprisingly, the polar ether 2MeTHF (91% yield) was among the best solvents, as previous studies were performed in THF (88% yield).[14f] Interestingly, excellent yields of 93% were also obtained in some nonpolar hydrocarbons (γ-terpinene, α-pinene), while other nonpolar hydrocarbons (limonene, 56%), ethers (methylal, 45%; ethylal, 64%; acetal, 55%; rose oxide, 36%; eucalyptol, 82%), and carbonates (DEC, 45%) provided low to moderate yields. In nonpolar carbonate DMC, instead of *tert*-butoxycarbonylation, the product of methoxycarbonylation was isolated in 93% yield (Chart 3, Scheme 4). This was the only observation where the solvent was chemically transformed in the reaction. Similar transesterifications were not observed for the other carbonates (DEC, PC, EC). Polar solvents (dimethyl isosorbide, 30%; GVL, 64%; PC, 60%; EC, 30% yield) were less efficient.

As for aminocarbonylation, we screened the top three best solvents (2MeTHF, α-pinene, and γ-terpinene) for alkoxycarbonylations of several substrates (Chart 3, Scheme 3). These studies revealed that the choice of solvent is dependent on the substrate. 2MeTHF was the best solvent for the products 7c (52%) and 7d (45%). The best yields of 7b were seen in γ-terpinene (98%), whereas γ-terpinene was not a good reaction media for the product 7f (44%). α-Pinene appeared to be the best solvent for the products 7a (93%) and 7f (51%) and in general showed good performance for most of the substrates.

The following investigation of the scope of *tert*-butoxycarbonylation in α-pinene as solvent showed that both electron-rich and -deficient aryl bromides can be effectively transformed into the corresponding products in moderate to good yields (Scheme 3). The best yields were observed for *tert*-butoxycarbonylation of electron-rich aryl bromides (7a, 93%;

7b, 91%; 7e, 80%; 7g, 85%; 7h, 90%; 7i, 93%). It should be noted that aryl bromides possessing electron-withdrawing groups and electron-deficient 3-bromopyridine were less effective and gave products in moderate yields (7c, 45%; 7d, 25%; 7f, 51%). Similar observations were reported by Skrydstrup et al. for alkoxycarbonylations performed in THF.[14f] Overall, our studies indicate that for alkoxycarbonylations, renewable solvents perform on the same level and, in some cases, even better than previously reported nonrenewable solvents.[10,14] Renewable solvents such as 2MeTHF, DMC, α-pinene, and γ-terpinene can be useful alternatives for trimethylamine, hexafluoroisopropanol, THF, toluene, and dimethyl sulfoxide frequently used for alkoxycarbonylation reactions.[14]

Studies on the Alkoxycarbonylation in DMC. In general, alkoxycarbonylation reactions rely on the use of bulky alcohols, phenols, or corresponding alkoxides.[14] Alcohols possessing α-hydrogens have found limited applications because of the side processes associated with β-hydride elimination.[14b,d] Therefore, we had a closer look at the methoxycarbonylations observed in DMC. The scope of the reaction was briefly studied on a range of substituted aryl bromides (Scheme 4). The reaction gave good yields for electron-rich 4-bromoanisole (8b 90%) and 4-bromotoluene (8d, 80%) as well as for 2-bromonaphthalene (8a, 93%) and 6-bromoquinoline (8e, 93%). Moderate yields were observed for electron-deficient aryl bromides (8c, 58%). For most of the products in Scheme 4, traces of *tert*-butoxycarbonylation were seen along with the main methoxycarbonylation product.

To gain a better understanding of the mechanism of the observed methoxycarbonylation, we performed a set of control experiments (Scheme 5). The *tert*-butyl ester 7a was

Scheme 4. Scope of Methoxycarbonylation of Aryl Bromides
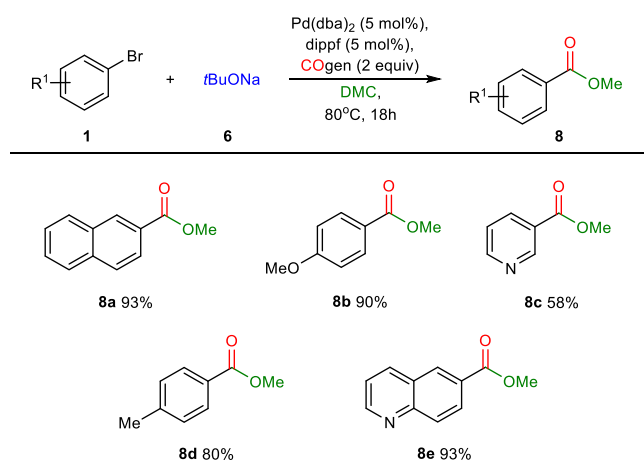
Scheme 5. Control Experiments to Elucidate the Formation of Methoxycarbonylated Products
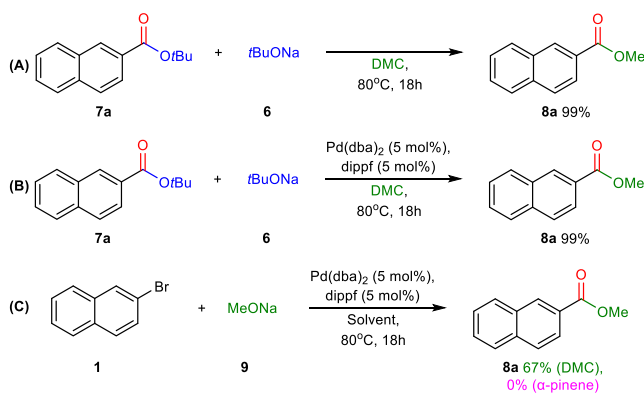
transformed into corresponding methyl ester **8a** in quantitative yield when treated with NaO*t*Bu in DMC. The transesterification took place in the presence and absence of the Pd-catalyst (Scheme 5A, B). In addition, the Pd-catalyzed methoxycarbonylation of 2-bromonaphthalene with sodium methoxide in DMC provided the methoxycarbonylated product in 67% yield, while an equivalent experiment in α-pinene did not lead to methoxycarbonylation (Scheme 5C). These findings indicate that two different reaction pathways may contribute to the formation of methoxycarbonylated products: (i) the Pd-catalyzed alkoxycarbonlyation with *tert*-butoxide followed by a transesterification with sodium methoxide generated *in situ* from the reaction of excess sodium *tert*-butoxide with DMC and (ii) the Pd-catalyzed methoxycarbonylation with *in situ*-generated sodium methoxide.

CONCLUSIONS

We have shown that Pd-catalyzed carbonylative transformations can be conducted in biomass- and CO_2-derived solvents with exceptionally high efficiency. A vast array of renewable solvents was analyzed for this purpose, including both well-established (2MeTHF, GVL, limonene, *p*-cymene, DMC, DEC, PC, and EC) and recently introduced solvent candidates (acetal, dimethyl isosorbide, γ-terpinene, α-pinene, eucalyptol, rose oxide, methylal, and ethylal). The work covered Pd-catalyzed carbonylative coupling of boronic acids and aryl bromides, aminocarbonylation and alkoxycarbonyla-

tion. For each of these transformations, we have found several renewable solvents, which can successfully substitute traditional nonrenewable solvents. For carbonylative coupling of boronic acids and aryl bromides the best results were observed in limonene and *p*-cymene. Aminocarbonylation worked well in DMC, α-pinene, and limonene, whereas the best solvents for alkoxycarbonylation turned out to be 2MeTHF, α-pinene, γ-terpinene, and DMC. Most of the known methodologies on alkoxycarbonylation are limited to bulky alkoxides and alcohols. We could show that this drawback can be overcome by the use of DMC, which led to methoxycarbonylated products. Finally, yet importantly, aminocarbonylation in renewable solvents can be used for the production of commercial drug Trimetozine and an analogue of Itopride.

EXPERIMENTAL METHODS

General Considerations. Solvents used in the work are purchased from Sigma-Aldrich if not otherwise stated. 2MeTHF (anhydrous, ≥99%, inhibitor-free, 673277-1L), methylal (absolute, over molecular sieve, ≥99.0%, 47676-250ML), ethylal (absolute, over molecular sieve, ≥99.0%, 47675-500ML-F), DMC (anhydrous, ≥99%, 517127-1L), DEC (anhydrous, ≥99%, 517135-1L), PC (anhydrous, 99.7%, 310328-1L), and EC (anhydrous, 99%, 676802-1L) were bought as anhydrous solvents equipped with a septa. Other renewable solvents were reagent grade; they were degassed, kept over activated molecular sieves (4 Å) for at least a week before use and stored under an Ar atmosphere. The purity of the solvents used in the work were as follows: acetal (99%, inhibitor-free, A902-500ML); dimethyl isosorbide (98%, inhibitor-free, 247898-100G); GVL (99%, V403-500G); γ-terpinene (97%, 223190-100ML); α-pinene (98%, 147524-250ML); limonene (97%, 183164-100ML); *p*-cymene (99%, C121452-1L); eucalyptol (99%, inhibitor-free, C80601-500ML); and rose oxide (97%, inhibitor-free, TCI, M2363-25G).

2MeTHF, acetal, dimethyl isosorbide, eucalyptol, rose oxide, methylal, and ethylal are ethers and may form peroxides when stored under air. However, peroxide tests (test strips for peroxide, MQuant, Supelco, VWR/Merck 1.10081.0001) of freshly bought solvents did not show any noticeable levels of peroxides. Acetal, methylal, and ethylal can be hydrolyzed in the presence of strong acids when heated. Under basic conditions, which are frequently used for the reactions involving organometallics, acetal, methylal, and ethylal are stable. GVL, DMC, DEC, PC, and EC can be hydrolyzed in the presence of strongly basic water solutions; under anhydrous conditions, they are stable. γ-Terpinene, limonene, and eucalyptol can be converted to *p*-cymene when heated above 220 °C.[4b] Overall, the examined renewable solvents appeared to be stable under the conditions used in the work. We have not observed the formation of side-products, for example, originating from hydrolysis of the carbonates, ethers, and esters used as solvents in the work (an exception was alkoxycarbonylation in DMC). It should be noted that the oxidation products of terpenes can be allergens.[9]

The reactions were performed in the previously reported two-chamber system (COware with total volume 20 mL, Supporting Information Figure S1) under an argon atmosphere, and a glovebox was employed for weighing out the reagents.

Warning! Most of the reactions were performed in specialized glassware under pressure. The glassware should

always be examined for damages before any manipulation. All laboratory safety procedures must be followed strictly and the work with pressure tubes must be conducted behind a shield.

General Procedure for Pd-Catalyzed Carbonylative Coupling of Boronic Acids and Aryl Bromides (Scheme 1). Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), boronic acid (1.2 equiv), Pd(acac)$_2$ (5 mol %), cataCXium AHI (10 mol %), 1 M NaOH (500 μl), and corresponding dry solvent (3 mL). The reaction mixtures consisted of an organic and an aqueous layer. Precipitation of palladium was not observed.

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol %), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP·HBF$_4$) (5 mol %), DIPEA (3 equiv), and 1,4-dioxane (3 mL). The two-chamber system was closed tightly with suitable caps and Chamber B was stirred at 80 °C until the release of CO was stopped. This was followed by stirring of both chambers at 80 °C for 18 h. The resulting mixture of Chamber A was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane:EtOAc (9:1) eluent.

General Procedure for Pd-Catalyzed Aminocarbonylation (Scheme 2). Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), amine (1.5 equiv), Pd(OAc)$_2$ (2 mol %), XantPhos (2 mol %), triethylamine (3 equiv), and corresponding dry solvent (3 mL). At the onset of the reaction, the mixture was homogeneous, while precipitation of palladium species (Pd-black) was observed during the course of the reaction both in conventional and renewable solvents.

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol %), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP·HBF$_4$) (5 mol %), 1,4-dioxane (3 mL), and DIPEA (3 equiv). Addition of DIPEA initialized the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80 °C for 18 h. The resulting mixture of Chamber A was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane:EtOAc (9:2) eluent.

General Procedure for Pd-Catalyzed Alkoxycarbonylation (Schemes 3 and 4). Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), *t*BuONa (1.5 equiv), Pd(dba)$_2$ (5 mol %), 1,1′-bis(diisopropylphosphino)-ferrocene (dippf) (5 mol %), and corresponding dry solvent (3 mL). At the onset of the reaction, the mixture was homogeneous, while precipitation of palladium species was observed during the course of the reactions both in conventional and renewable solvents.

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol %), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP·HBF$_4$) (5 mol %), 1,4-dioxane (3 mL), and DIPEA (3 equiv). Addition of DIPEA initialized the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80 °C for 18 h. The resulting mixture of Chamber A was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane:EtOAc (9:1) eluent.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00325.

Detailed description of experiments and results, analytical and spectroscopic data (PDF)

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Author Contributions

The manuscript was written through contributions of all the authors. All the authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): T.S. is co-owner of SyTracks A/S, which commercializes the two-chamber system (COware) and COgen.

■ ABBREVIATIONS

2MeTHF,2-methyltetrahydrofuran; Acetal,1,1-diethoxyethane; COgen,9-methyl-9*H*-fluorene-9-carbonyl chloride; COware,two-chamber reactor; cataCXium AHI,di(1-adamantyl)-*n*-butylphosphine hydriodide; DMC,dimethyl carbonate; DEC,-diethyl carbonate; DIPEA,*N*,*N*-diisopropylethylamine; dippf,1,1′-bis(diisopropylphosphino)ferrocene; EtOAc,ethyl acetate; EC,ethylene carbonate; GVL,γ-valerolactone; LCA,-life-cycle assessment; PC,propylene carbonate; Pd-(acac)$_2$,palladium(II) acetylacetonate; Pd(OAc)$_2$,palladium(II) acetate; Pd(dba)$_2$,bis(dibenzylideneacetone)palladium(0); TTBP·HBF$_4$,tri-*tert*-butylphosphonium tetrafluoroborate; XantPhos,4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; XantPhos Pd G3,[(4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate

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