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Palladium-catalyzed synthesis of mixed anhydrides *via* carbonylative telomerization†

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For the first time, mixed carboxylic anhydrides were accessed directly *via* homogeneous palladium catalysis from 1,3-butadiene and carboxylic acids. Under carbonylative telomerization conditions, the respective mixed 3,8-nonadienoic anhydrides are formed in a single reaction step with yields of up to 82%. These very reactive mixed anhydrides can then be used for consecutive reactions in a one-pot manner and selectively transfer the newly formed unsaturated C9 unit. Possible changes in the proposed mechanism were discussed and in a first example, the mixed anhydrides were utilized to form amides.

Introduction

Due to the rising demand for energy, developing more efficient ways to convert basic feedstock into novel products has become a critical challenge. Hence, the direct use of simple building blocks, such as 1,3-butadiene and carbon monoxide, is of high interest. One of the most relevant tools enabling such efficient conversions is catalysis and particularly homogeneous catalysis.[1] Compared to heterogeneous catalysis, it offers mainly higher activity due to the lack of mass transfer limitations.[1] Additionally, the catalytic mechanism can be studied more easily, and its detailed understanding enables the development of new reactions and more sophisticated reaction designs.[1] This possibility offers excellent potential for addressing the challenges mentioned above and synthesizing complex molecules in as few steps as possible.

In 1971, Billups discovered in collaboration with Union Carbide Corporation the homogeneously catalyzed carbonylative telomerization (Fig. 1).[2] They investigated the carbonylation of dienes and it was reported that halide-free palladium catalysts, such as Pd(acac)$_2$, give ethyl nona-3,8-dienoate from 1,3-butadiene and ethanol in the presence of carbon monoxide and PPh$_3$ as ligand.[2] They showed that the ester is directly formed from 1,3-butadiene and not by carbonylation of the ether, the telomerization product of 1,3-butadiene and ethanol.[2] This multi-component reaction was later named "carboxytelomerization" due to the newly formed carboxylate group. Remarkably, four molecules react

in a single catalytic cycle to form the final product, mediated by a single catalyst complex (Fig. 1), which offers a highly efficient and atom-economic $2 + 2 + 1 + X$ synthesis route starting from basic chemicals.[2,3]

Eight years later, in 1979, Knifton published a more comprehensive study on the Pd-catalyzed carboxytelomerization.[3] With monodentate phosphine ligands, high yields and selectivities were achieved in *N*-heterocyclic or tertiary arylamine solvents, presumably due to increased catalyst stability. Until then, the reaction was limited to 1,3-butadiene and short-chain aliphatic alcohols as substrates.[2–5] In 2018, Vogelsang *et al.* were able to connect the carboxytelomerization to an additional carbonylation. They developed a protocol for synthesizing a linear, terminal C10-diester from 1,3-butadiene, methanol and carbon monoxide in a one-pot manner.[6] Following this "rediscovery" of carbonylative telomerization, several other papers were published, exploring the scope of that particular reaction for the first time. Carboxytelomerization converts the renewable β-myrcene in quantitative yields into highly branched esters, with best results in the absence of additional solvents,[7] which resembles the first diene used, other than 1,3-butadiene. Furthermore, Vogelsang *et al.* reported the conversion of amines under carbonylative telomerization conditions for the first time.[8] Inspired by the resulting products, this reaction was named amidotelomerization. It offers a one-step synthesis for unsaturated C9-amides, otherwise synthesized in a multistep reaction associated with high waste production.[8,9] All these examples show the high potential of carbonylative telomerization reactions to produce unsaturated C9-esters and their derivatives. However, some nucleophiles remain challenging to convert efficiently. On the one hand, phenols and tertiary alcohols are less active in carbonylative telomerization and result in low yields. On the other hand,

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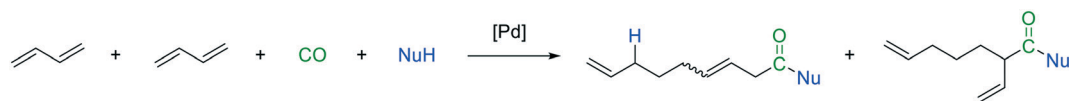
Fig. 1 Pd-Catalyzed carbonylative telomerization of 1,3-butadiene.

amines required a high catalyst loading for their conversion in carbonylative telomerization.[7,8,10]

In the same year, Sauthier and co-workers showed the positive influence of carboxylic acids on carboxytelomerization. They proposed a cationic palladium complex (Fig. 2, right) that plays a critical role in converting phenols, as it allows soft nucleophiles such as phenols to cleave the product from the palladium catalyst more efficiently, resulting in higher yields.[10] In 2019, they applied their system to different di- and polyols and different bio-based alcohols.[11] Recently, similar results were achieved by Vogelsang et al., who also synthesized di- and triesters but under acid-free conditions. Additionally, they were able to control the degree of esterification via control over the 1,3-butadiene concentration.[12] These di- and triesters can be used as synthetic fats, lubricants or polymer precursors.

So far, two different reaction mechanisms have been proposed for the carbonylative telomerization. The first was proposed by Billups[2] and was later refined by Knifton (Fig. 2, left).[3]

Similar to the mechanism of a "simple" telomerization reaction, the first step represents an oxidative coupling of two 1,3-budadiene molecules forming the allyl complex **B**. Insertion of CO into the σ-allyl C–Pd bond forms the acyl complex **C**. This species is then attacked by the alcohol nucleophile to form the intermediate **D**, which collapses via a reductive elimination into the desired ester product and the active catalyst complex **A**.[3]

Sauthier et al. proposed a different mechanism for the carbonylative telomerization of phenols (Fig. 2, right cycle).[10] Phenols result in low yields under common carbonylative telomerization conditions. The key for this transformation was the addition of benzoic acid. Therefore, a cationic Pd-complex was proposed. Due to its positive charge, the complex supposedly becomes more electrophilic increasing the interaction with the phenol nucleophile. In their mechanism, the complex **B** is protonated by the acid and forms the cationic complex **E** upon coordination of CO. The CO then undergoes a migratory insertion into the η^3-allyl C–Pd bond forming **F**. In the last step, the phenol cleaves the ester from the Pd-complex, while restoring the active catalyst **A** as well as a proton.[10]

Within our longtime interest in developing novel and sustainable catalytic synthesis strategies, we set ourselves the goal to further expand the valuable synthesis tool carbonylative telomerization. In this context, the implementation of new nucleophiles is of particular interest since entirely new classes of compounds would be accessible for further applications. Here, it is of interest to consider the closely related telomerization reaction.[13,14] The telomerization is complemented by its carbonylative counterparts for many nucleophiles (Fig. 3), such as alcohols and amines. However, for carboxylic acids, which are well-known nucleophiles for telomerization (Fig. 3),[15–19] the carbonylative counterpart is not yet described in the literature. Thus, four substrate molecules under carbonylative telomerization conditions, including the
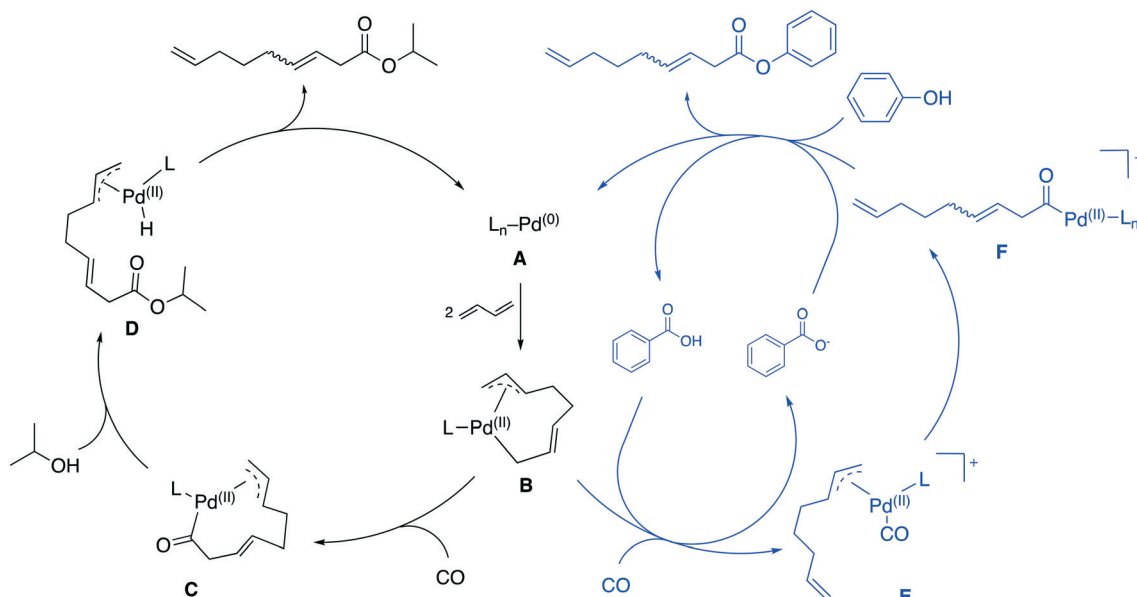

Fig. 2 Catalytic cycles proposed for the carboxytelomerization proposed by Knifton (left),[3] and Sauthier (right).[10]
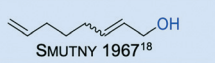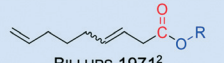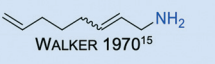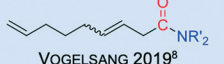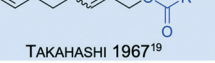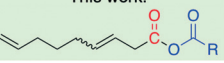
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Paper

Fig. 3 Accessible products from 1,3-butadiene and different nucleophiles under telomerization (left) and carbonylative telomerization (right) conditions, respectively.

carboxylic acids, would be transformed into mixed unsaturated C9-anhydrides in a single reaction step in the presence of a palladium catalyst. Such a synthesis method is particularly interesting, since mixed carboxylic anhydrides are highly reactive intermediates with a broad range of applications. Surprisingly, best to our knowledge, no transition metal-catalyzed synthesis for mixed carboxylic acid anhydrides from dienes was reported until now.

Mixed carboxylic acid anhydrides are often used to activate otherwise weakly reactive carboxylic acids. A prominent example for the application of mixed anhydrides is the Yamaguchi esterification, which utilizes 2,3,6-trichlorobenzoic acid chloride to form a mixed anhydride with the carboxylic acid to be activated. The anhydride can react with an alcohol to form the desired ester in high yield and selectivity in a second reaction step.[20] A major drawback of such syntheses, and the synthesis of mixed anhydrides in general, is the necessity of acid chlorides as substrates, which is associated with the production of stoichiometric amounts of waste products, *i.e.* salts.[21,22]

Herein, we present a novel Pd-catalyzed synthesis of mixed carboxylic acid anhydrides *via* carbonylative telomerization of 1,3-butadiene and carboxylic acids. Additionally, the corresponding anhydrides are implemented in consecutive reactions.

Experimental section

Carbonylative telomerization

First, the acid was weighed into the autoclave's 20 mL stainless steel vessel. The reactor was closed, then evacuated and purged with argon. A solution containing Pd(OAc)$_2$ (6.74 mg, 0.03 mmol, 1 mol%) and PCy$_2$Ph (17.3 mg, 0.06 mmol, 2 mol%), 3 mL dry dioxane and the internal standard *n*-decane (75 mg, 0.527 mmol) was prepared. Pd(OAc)$_2$ and

PCy$_2$Ph were weighed into a 20 mL headspace vial, sealed with a crimp cap, and then alternately evacuated and purged with argon. The corresponding amount of solvent and internal standard was added *via* syringe. The mixture was placed in an ultrasonic bath for homogenization and then transferred to the reactor *via* syringe under argon counterflow. 1,3-Butadiene was condensed under auto-pressure into a PTFE tube. Afterwards, the tube was connected to the reactor, and 1,3-butadiene was transferred into the reactor. The correct amount was adjusted *via* differential weighing. The reactor was pressurized with carbon monoxide, placed in a heating block, and magnetically stirred for 20 h.

After 20 h, the reactor was cooled on water/ice, depressurized and purged with argon. Piperidine (1032 mg, 12 mmol, 4 eq.) was added to the reaction mixture *via* syringe under argon counterflow. The solution was stirred for 5 h at 50 °C. Then it was cooled, and the solvent was removed under reduced pressure. The residue was dissolved in 10 mL dichloromethane and extracted with 20 mL diluted sulfuric acid (5 v%). The aqueous phase was then extracted twice with 10 mL dichloromethane. The combined organic phases were dried with MgSO$_4$ and concentrated under reduced pressure. The residue was dissolved in 15 mL diethyl ether and extracted with 30 mL of a 0.5 M NaOH solution. The aqueous phase was extracted two more times with 20 mL diethyl ether. The combined organic phases were dried with MgSO$_4$. Two spoons of celite were added, and the mixture was concentrated under reduced pressure until dry. The resulting powder was further purified using a 40 g "Flash Pure" cartridge (ethyl acetate : cyclohexane, 1% to 10% in 2 CV, 10% until eluted).

Exclusion of alternative pathways

3,8-Nonadienoic acid (467 mg, 3 mmol, 1 eq.) was weighed into a 20 mL stainless steel reactor. The reactor was closed, then evacuated and purged with argon. The palladium precursor Pd(OAc)$_2$ (6.74 mg, 0.03 mmol, 1 mol%) and PCy$_2$-Ph (17.3 mg, 0.06 mmol, 2 mol%) were weighed into a 20 mL headspace vial and sealed with a crimp cap. The vial was then alternately evacuated and purged with argon while connected to a Schlenk-line *via* a cannula. The corresponding amount of dry dioxane (3 mL) was added to the vial *via* syringe. The mixture was placed in an ultrasonic bath until a uniform solution was observed. Then the solution was transferred to the reactor *via* syringe under argon counterflow. Piperidine (1032 mg, 3 mmol, 4 eq.) and 75 mg
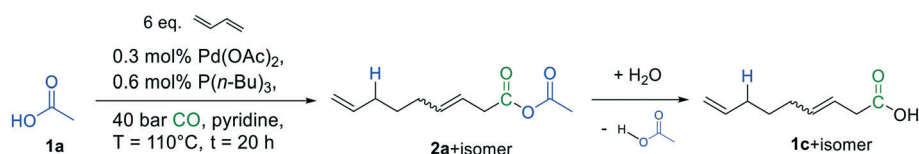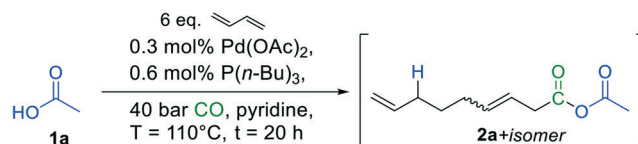

Fig. 4 Initial reaction conditions for carbonylative telomerization of 1,3-butadiene with acetic acid.
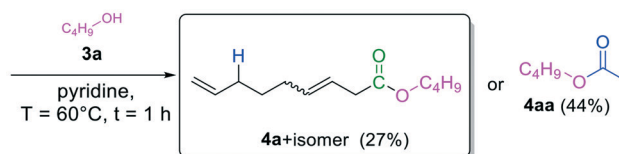
Carbonylative telomerization:

Derivatization:

Fig. 5 Synthesis of butyl nona-3,8-dienoate **4a** by carbonylation telomerization of 1,3-butadiene with acetic acid and subsequent derivatization.

of the internal standard *n*-decane were added to the reactor *via* syringe under argon counterflow. The reactor was stirred for 5 h at 50 °C. Afterwards, the reaction was stopped by an ice bath, and the reaction mixture was analyzed *via* GC–FID.

Results and discussion

The experiments were initially carried out employing 1,3-butadiene in combination with glacial acetic acid **1a** as model substrates, as the latter is a well-known nucleophile in the related telomerization reaction.[15,17,18] Carbonylative telomerization conditions (Fig. 4) were adapted from our previous studies,[6] and applied using a 20 mL stainless steel autoclave with magnetic stirring. The catalyst was *in situ* generated from Pd(OAc)$_2$ as the precursor and the ligand tri-*n*-butyl phosphine.

The reaction was examined *via* GC–MS (see ESI†). To our delight, analysis of the spectra indicated the presence of the desired mixed anhydride **2a** beside one main isomer, presumably its branched isomer. Additionally, two derivatives of 3,8-nonadienoic acid (**1c** + isomer) were detected, which may have formed by hydrolysis of the mixed anhydrides, underlining the expected high reactivity of the formed product. Consequently, isolation of **2a** *via* standard purification methods such as chromatography is rather tricky and complicates its precise quantification.

However, this high reactivity allows easy derivatization into more stable compounds, quantified with more precision. Hence, carbonylative telomerization was repeated with acetic acid, but after depressurizing the reactor, butyl alcohol **3a** was added as the nucleophile (Fig. 5) before the analysis. The corresponding esters could be readily detected *via* GC–MS and were quantified by GC–FID.

Under these non-optimized conditions, however, yields were not satisfactory yet. The corresponding acetate **4aa**, resulting from a nucleophilic attack of the alcohol on the

acetate side of the anhydride, was the main product. Since more straightforward and effective acylating agents are available, it is not favorable to transfer the acetic acid side of the mixed anhydride to the nucleophile. Instead, transfer of the 3,8-nonadienoic acid part of the anhydride to the nucleophile is desired. In this way, it is possible to produce valuable unsaturated products that can be readily functionalized further due to their terminal double bond. Moreover, if the transfer of the 3,8-nonadienoic acid part of the anhydride to the nucleophile is selective, the initial acid **1a** is reformed, offering potential reuse.

The relatively low selectivity can be explained by the nature of the formed mixed anhydride **2a**: the acid functionalities in acetic acid and nonadienoic acid have a similar pK_a-value and nucleophilicity since both are aliphatic acids. High selectivity may be achieved if one of the acid groups is a significantly better leaving group. For instance, acids having a lower pK_a-value are usually better leaving groups. Another option would be the use of resonance stabilized acids such as benzylic acid derivatives. A well-known reaction making use of this concept is the Yamaguchi esterification.[20] The reaction results in rapid and highly selective formation of esters from carboxylic acids by activation through a mixed anhydride. In this case, electron-poor benzoic acid derivatives are used to increase the reactivity and selectivity drastically. Benzoates are resonance stabilized; therefore, they are better leaving groups than non-aromatic acid anions. Hence, benzoic acid (**1b**) was used, providing a more stable leaving group, aiming for higher selectivity.

Improvement and validation of the system with benzoic acid (1b)

Benzoic acid (**1b**) was chosen as the nucleophile and was tested under carbonylative telomerization conditions (Fig. 6).

GC–MS analysis revealed the presence of the mixed carboxylic anhydride. A small amount of the product could be separated *via* chromatography with an isolated yield of 6%
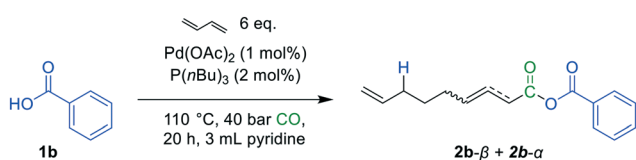

Fig. 6 Carbonylative telomerization of 1,3-butadiene with benzoic acid (**1b**).
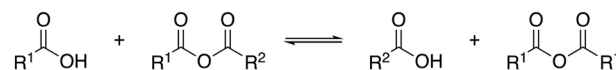

Fig. 7 Disproportionation reaction of a mixed anhydride to the corresponding symmetrical anhydrides.[26]

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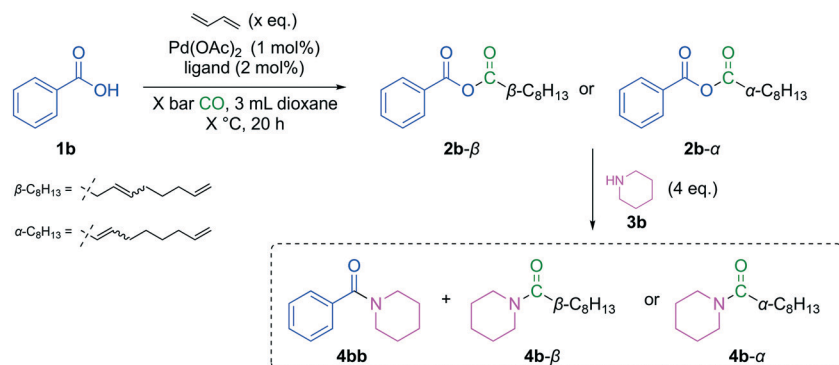*Catal. Sci. Technol.*, 2022, **12**, 3992–4000 | **3995**

Fig. 8 Carbonylative telomerization of 1,3-butadiene with benzoic acid (**1b**) for the synthesis of mixed anhydrides (**2b**) prior to optimization and subsequent derivatization yielding amides for quantification.

using dry solvents. The presence of anhydrides was confirmed by FT-IR (see in ESI†), indicating the success of the reaction. NMR spectra of the product revealed the isomerization of the β-unsaturated product **2b**-β to the α-unsaturated isomer of **2b**-α (see in ESI†). This isomer seems to be more stable, presumably due to the conjugated double-bond and therefore could be isolated. The formation of the conjugated isomer of **2b** could be promoted by the acidic reaction environment, which can lead to Pd–hydride species. These species are known for their isomerization activity.[23–25]

The corresponding symmetrical anhydrides, *i.e.* benzoic acid anhydride and nonadienoic acid anhydride, respectively, were detected during GC-analysis. Presumably, the highly reactive mixed anhydrides undergo disproportionation reactions under the high temperatures in the GC injecting block, yielding an equilibrium of the two symmetrical and the mixed anhydride (Fig. 7).[26–28] We strongly assume that symmetrical anhydrides are not formed during carbonylation telomerization. However, this must be excluded for precise quantification, and a different analysis protocol must be developed.

For quantitative analysis of mixed anhydrides formed *via* carbonylative telomerization under our initial conditions, a nucleophile was added to the reaction mixture after stopping (ice bath and depressurization) (Fig. 8). Next, amines were added for derivatization, which are more nucleophilic compared to the initially applied alcohols. The reaction mixture was analyzed afterwards *via* GC–FID, and the corresponding amides were quantified.

After a short screening of potent amines (see in ESI†) and the corresponding reaction conditions for the derivatization step, piperidine (**3b**) was chosen as a suitable candidate resulting in the highest total amide yield of 67% after a reaction time of 5 h. An excess of 4 equivalents of **3b** was applied to ensure a complete amidation of the mixed anhydrides. Additionally, dioxane was adapted as the solvent form Sauthier *et al.* since it already had proven to be beneficial for carbonylative telomerization in the presence of acids and will avoid pyridinium salt formation.[10] This sequential reaction set up was used in the following to optimize the carbonylative telomerization of benzoic acid (**1b**) regarding the amount of 1,3-butadiene, the ligand, the CO pressure and the temperature (Fig. 8).

It is important to exclude other reaction pathways towards the analyzed amides, as this would lead to false quantification of the mixed anhydrides. We tested whether amides **4b** and **4bb** may be formed by direct reactions between the acid and the amine (Fig. 9) to validate the chosen analysis method consisting of derivatization and quantification of the resulting amides. 3,8-Nonadienoic acid (**1c**) was included since it can be a by-product of the side reaction towards **4bb**.

In both cases, no amides were detected. Hence, all amides from the derivatization step result from the reaction of the mixed anhydride and the amine. Their combined yield can thus give precise information about the yield of the mixed anhydride formed *via* carbonylative telomerization.
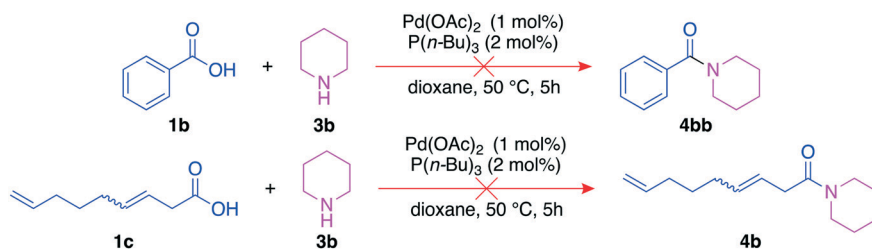

Fig. 9 Exclusion experiments with benzoic acid **1b** and 3,8-nonadienoic acid **1c**.

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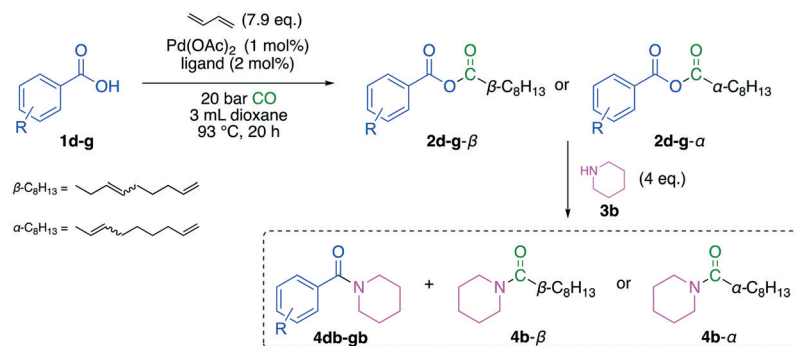This journal is © The Royal Society of Chemistry 2022

Fig. 10 Applied substituted benzoic acid derivates.

Optimization *via* DoE

Having an established protocol for quantifying carbonylative telomerization in hand (Fig. 8), this set-up was used to optimize the reaction conditions *via* a design of experiments (DoE) towards an increased anhydride yield.

Previous investigations on carbonylative telomerization reactions have revealed significant parameters, such as temperature, CO pressure and the excess of 1,3-butadiene. These factors were varied in the ranges stated in Table 1, taking other research on these reactions into account. Additionally, the ligand plays a crucial role regarding reaction yield. Knifton has initially shown that basic monodentate phosphines resulted in good to excellent yields, and Vogelsang *et al.* have shown the positive effects of large Tolman angles.[3,7] Therefore, P(*n*-Bu)$_3$, PPh$_3$ and PCy$_2$Ph were chosen for this investigation; all other parameters were kept constant (see Fig. 8).

The sum of the detected amides after derivatization was considered the anhydride yield, hence the output for the DoE. A central composite face-centered design was chosen using the optimization software Modde©, which resulted in a total of 27 experiments, each carried out as duplicates (see in ESI†). The data was evaluated, and the model had to be changed for better results to enhance the accuracy of the prediction. The calculations revealed that the CO pressure was not a significant factor in the given ranges. It was thus excluded from further calculations. Therefore, the pressure was set to 20 bar, as it represents the mildest reaction condition.

The calculations made by Modde© applied to the resulting dataset suggested a reaction temperature of 93 °C, and excess of 7.9 eq. 1,3-butadiene and PCy$_2$Ph as the ligand. The predicted yield was calculated to be 76%. These results were verified by the corresponding experiments using the optimized reaction conditions, which resulted in good

reproducibility since the duplicates show high similarity (Table 2, entry 1 and 2). The yield distribution of the derivatized products under optimized reaction conditions showed good reproducibility (Table 2). The sum of amides, in this case, equals the yield for the desired mixed anhydride intermediates 2b-β and 2b-α, showing an average yield of the mixed anhydride of 80%, which is 4% higher than predicted. Moreover, the desired amides 4b-β and 4b-α account for over 70% of the total amide yield. Consequently, the mixed anhydride favors the transfer of the aliphatic acyl rest (*i.e.* 3,8-nonadienyl) to the amide yielding linear and branched C$_9$-amides. The optimization was carried out using calculated response factors using an established estimation method.[29] Afterwards, the products were isolated to confirm the calculated results (Table 2, entry 3).

Implementation of optimized conditions

Afterwards, the optimized conditions were applied to a small scope investigation (Fig. 10). Since the electronic nature of benzoic acid derivatives is mainly influenced by substituents on the aromatic ring, different electron-withdrawing and donating groups were tested (Table 3). In this investigation, two effects must be considered. First, the nucleophilicity of the acid influences the reactivity in carbonylative telomerization. And second, the reactivity of the resulting anhydride is again influenced by the nature of the benzoic acid. An electron-deficient acid is an excellent leaving group. If the anhydride consists of two very different acid groups in pK_a, it becomes more reactive. The electron-rich acid is transferred preferentially in a consecutive reaction, as seen in Yamaguchi esterification.[20] Since the requirements for both reaction parts are opposing, a trade-off has to be found with

Table 1 Factor settings for the DoE

Factor	Temperature [°C]	CO pressure [bar]	1,3-Butadiene eq. [–]	Ligand (Tolman angle)
Minimum	80	20	4	P(*n*-Bu)$_3$ (132°)
Middle	100	30	6	PPh$_3$ (148°)
Maximum	120	40	9	PCy$_2$Ph (164°)
Optimized	93	20	7.9	PCy$_2$Ph (164°)

Table 2 Anhydride yield under optimized conditions compared to predicted yield

Entry	Predicted yield [%]	$\sum Y$ [%]	Y (4b-β) [%]	Y (4b-α) [%]	Y (4bb) [%]
1	76	79	36	20	23
2	76	82	37	22	23
3[a]	76	81	37	20	24

Conditions: carbonylative telomerization: 3 mmol benzoic acid, 23.7 mmol (7.9 eq.) 1,3-butadiene, 1 mol% Pd(OAc)$_2$, 2 mol% PCy$_2$Ph, 3 mL dioxane, 20 bar CO, 93 °C, 20 h, 600 rpm. Internal standard 75 mg decane; derivatization: 12 mmol piperidine, 50 °C, 5 h, 600 rpm. Yields (Y) were determined *via* GC-FID analysis using *n*-decane as an internal standard and calculated with respect to the carboxylic acid. [a] Isolated yield.

high reactivity in carbonylative telomerization and satisfactory selectivity of the consecutive reaction.

The highest yield of 91% can be achieved using anisic acid (**1e**). Due to the +−M-effect, anisic acid is electron-rich acid and therefore has a higher pK_a value. More electron-rich acids appear to be more reactive in carbonylative telomerization, showing higher overall anhydride yield. The anhydride yield is reduced with a lower pK_a value. In contrast, the selectivity of **4b** increases with a lower pK_a value. As mentioned before, electron-poor acids are better leaving groups and are more stable in their anionic form. All tested acids have a lower pK_a value than 3,8-nonadienoic acid (**1c**), which should be similar to nonanoic acid (was "pelargonic acid"), *i.e.* 4.96.[30] Hence, the 3,8-nonadienoic rest is preferably transferred to the nucleophile. This effect increases with larger differences in pK_a values and results in higher selectivity with a lower pK_a. For **1f**, it was impossible to isolate the arylamide **4fb**, resulting in the highest selectivity for **4b**. Although the overall activity of **1f** is lower compared to the more electron rich acids, the selectivity towards the unsaturated C9-amides is high. This offers a way to selective pass the newly formed unsaturated C9-chain along to the consecutive product (Table 3, entry 4), since *p*-Cl-benzoate is the better leaving group. In comparison with the anhydride **2e** a selectivity of only 72% was achieved in the amidation reaction. For **1g**, only traces of the products could be observed, indicating low activity in carbonylative telomerization. These results can be explained with the lower nucleophilicity of electron poor carboxylic acids. Mayr *et al.* reported a nucleophilicity scale, showing *p*-nitro benzoate to be significant less nucleophilic than the benzoate ion.[31] The lower nucleophilicity renders the acid les reactive for the carbonylative telomerization, thus forming less of the corresponding anhydride. This shows a compromise has to be found, between a high reactivity in carbonylative telomerization resulting from electron rich carboxylic acids and an ideal anhydride for consecutive reaction built with electron poor carboxylic acids.[20] Additionally, the electronic properties of the acid have an influence on the formation of the α-unsaturated isomer **4b-α** and **2d–g-4b-α**, respectively. More electron-withdrawing groups in *para*-position of the acid result in a higher degree of isomerization and result in equal amounts of **4b-α** and **4b-β** (Table 3, entry 4), which is in contrast to more electron-rich acids, which result in 2 : 1 ratio of **4b-α** and **4b-β**. This aligns with the results found by Sauthier *et al.* for the carbonylative telomerization of phenols in the presence of catalytic amounts of benzoic acid.[10] This effect could also be emphasized, by the higher acidity of the *p*-Cl substituted benzoic acid, which could also lead to more Pd–H species forming and thus more isomerization.

Mixed carboxylic anhydrides are mainly utilized to form consecutive products, such as the here implemented amidation. However, a large excess of the nucleophile is typically not desirable. Previously, an excess of piperidine (**3b**) was introduced to the system to guarantee full conversion of the mixed anhydrides for quantification. Since carbonylative telomerization as the first step is now optimized, further investigations for the derivatization step were carried out. A sub-stoichiometric amount, *i.e.* 0.75 eq., of piperidine was applied. This results in a 1.1 eq. excess of the anhydride (Table 4).

The total yield of the desired product reaches 77%, and 23% of the piperidine is converted to other by-products. These by-products can be assigned to the formation of ammonium salts since unreacted acid readily reacts with piperidine to form piperidyl benzoate.

Table 3 Yield distribution for different substituted acids

Entry	R (acid)	pK_a (ref. 30)	$\sum$ yield [%]	Y (4b-β) [%]	Y (4b-α) [%]	Y (4db–gb) [%]
1	*m*-Me (**1d**)	4.28	85	39	22	24
2	*p*-OMe (**1e**)	4.49	91	40	26	25
3	*p*-OMe[a] (**1e**)	4.49	71	36	17	18
4	*p*-Cl (**1f**)	3.98	74	36	37	Traces[b]
5	*p*-NO$_2$ (**1g**)	3.42	—	Traces[b]	Traces[b]	—

Conditions: carbonylative telomerization: 3 mmol acid, 24 mmol 1,3-butadiene, 1 mol% Pd(OAc)$_2$, 2 mol% PCy$_2$Ph, 3 mL dioxane, 20 bar CO, 93 °C, 20 h, 600 rpm. Internal standard 75 mg decane; derivatization: 12 mmol piperidine, 50 °C, 5 h, 600 rpm. Isolated yield (*Y*) related to acid. [a] 0.5 mol% Pd(OAc)$_2$, 1 mol% PCy$_2$Ph; derivatization: 12 mmol piperidine, 50 °C, 5 h, 600 rpm. Isolated yield (*Y*) related to acid. [b] Not isolated.

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Table 4 Conversion of piperidine and yield distribution for 0.75 equivalents of piperidine

Entry	$\sum$ yield [%]	Y (4b-β) [%]	Y (4b-α) [%]	Y (4bb) [%]	X (3b) [%]
1	77	36	22	19	100

Conditions: carbonylative telomerization: 3 mmol benzoic acid, 23.5 mmol 1,3-butadiene, 1 mol% Pd(OAc)$_2$, 2 mol% PCy$_2$Ph, 3 mL dioxane, 20 bar CO, 93 °C, 20 h, 600 rpm. Internal standard 75 mg decane; derivatization: 2.26 mmol piperidine, 50 °C, 5 h, 600 rpm. Yield (Y) and conversion (X) related to amine determined *via* GC-analysis with decane as internal standard.

Proposed reaction mechanism

The best results in the carbonylative telomerization with carboxylic acids were achieved with the bulky, basic phosphine PCy$_2$Ph. Such donor phosphine ligands are reported to push the equilibrium of the η^3-allyl into a σ-allyl complex (**B**)[32] and an insertion of CO is preferred in this position, thus the carbonyl Pd complex **C** is formed, analogous to the proposed mechanism by Knifton (Fig. 11).

Two pathways for the interaction of the carboxylic acid are feasible pathways. On the one hand, the reaction continues the mechanism proposed by Knifton and forms a Pd–H while the carboxylate inserts in the Pd carbonyl bond (Fig. 11, path a)),[3] resulting in complex **G**. A reductive elimination of the allyl and the hydride forms the product and closes the catalytic cycle by releasing **A**. On the other hand, the acid could first protonate the remaining Pd–allyl and the resulting carboxylate could coordinate to the complex replacing the former allyl (Fig. 11, path b)). Again, a reductive elimination of the product forms the desired anhydride product and **A**. Both proposed pathways would proceed without a cationic catalyst species, since the insertion of CO into the σ-allyl–Pd bond is more likely compared to the migratory-insertion into a η^3-allyl–Pd bond.

Conclusion

A novel, palladium-catalyzed synthesis for mixed carboxylic acid anhydrides was developed. For the first time, it was possible to generate mixed anhydrides catalytically from bulk chemicals, namely 1,3-butadiene, CO, and benzoic acid derivatives. In addition, a quantification protocol was developed using amines for quantitative derivatization in combination with standard GC-analysis. It was possible to optimize the conditions for the anhydride synthesis using this protocol and yields up to 82% were achieved with the model substrate benzoic acid.

A small investigation of the scope of the reaction was carried out, including different benzoic acid derivatives. The experiments have shown the importance of the nature of the acid, as more electron-rich benzoic acid derivatives achieved higher total yields of up to 94% due to their higher nucleophilicity. In contrast, *p*-Cl-benzoic acid, which is less electron rich, resulted in only 74% yield in carbonylative telomerization, but the consecutive amidation was highly selective due to the better leaving group *p*-Cl-benzoate. Further investigations of the scope, including different dienes, are currently in progress, as well as other applications of the resulting anhydrides. Additionally, the mechanism must be studied in more detail, as the currently accepted proposed mechanism has to be updated for the conversion of carboxylic acids.
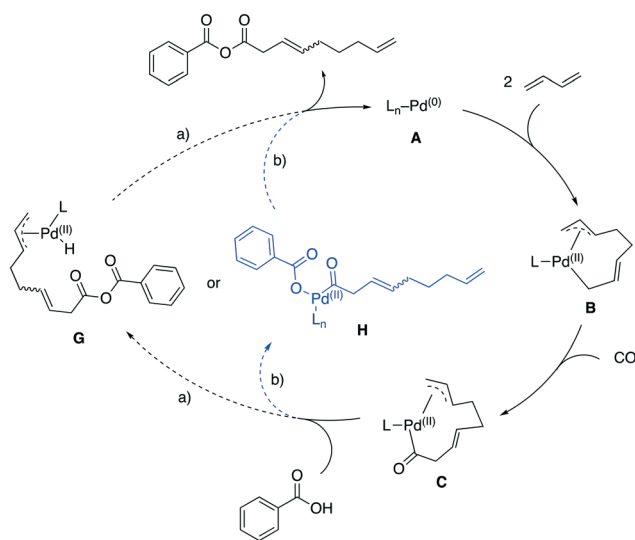
Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Fig. 11 Possible reaction mechanisms for carbonylative telomerization of 1,3-butadiene with benzoic acid.

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