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Palladium-Catalyzed Synthesis of Carboxylic Acid Anhydrides from Alkenes via *in situ* Generated Carboxylic Acids

Ashok Ramakrishnan^[a] and Elisabeth Bouwman^{*[a]}

We herein present a carbonylative strategy to synthesize carboxylic acid anhydrides from alkenes from *in situ* generated carboxylic acids. Formic acid (FA) reacts with alkene and CO under catalytic conditions to generate carboxylic acids. With our established palladium-based catalytic reaction conditions and modulating the alkene:formic acid ratio to at least 2:1, acid anhydrides were effectively generated from alkenes. The catalytic process was applied to various alkenes, simple as well

as with various functional groups, to give moderate to excellent yields as observed with NMR and upon isolation of the corresponding (linear) amide produced on derivatization. Furthermore, one-pot derivatization of the reaction mixtures provides direct access to various acyl-based molecules including phenolic esters, primary amides, thioesters and ketones, which otherwise require special conditions for their synthesis via carbonylation.

Introduction

Symmetric carboxylic acid anhydrides are vital electrophilic acylating reagents used in chemical synthesis of various fine chemicals, pharmaceuticals and polymers. The mild nature and effective chemical reactivity of anhydrides have established them as widely favored acylating agents in organic synthesis. As a result, they are employed, for example, as reagents in peptide chemistry to facilitate N-acylation processes.^[1] It is important to use symmetric acid anhydrides in acylation processes as it avoids the generation of by-products resulting from an attack on the undesired acyl group in mixed anhydrides.^[2]

Conventional synthesis of symmetric acid anhydrides involves the activation of carboxylic acids by reagents such as thionyl chloride,^[3] carbodiimides,^[4] and triphosgene;^[5] the use of these reagents generates by-products, and thus reduces the atom efficiency of the reaction. The development of metalcatalyzed carbonylation of alkenes with carbon monoxide as a cheap and abundant C1 feedstock has emerged as a sustainable and highly atom-economical synthesis for acyl-bearing molecules. Applying this concept, we established a facile palladiumcatalyzed carbonylative synthesis of carboxylic acid anhydrides from alkenes with carboxylic acid as co-substrates (hydroacyloxycarbonylation).^[6]

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Carbonylative synthesis of carboxylic acids (hydrocarboxylation) is one of the prominent reactions in carbonylation chemistry.^[7] Hydrocarboxylation of alkenes using formic acid (FA) in excess (at least 2.0 equivalents with respect to alkene) is one of the well-known synthetic strategies established and reported by several groups (Scheme 1a).^[8] The catalytic cycle involves formation of a mixed anhydride containing FA, which is known to be highly unstable and readily decomposes to release CO with formation of a carboxylic acid derived from the alkene. Taking this into account and based on the established catalytic conditions from our previous studies on catalytic generation of acid anhydrides (Scheme 1b), we envisaged a strategy to produce (symmetric) carboxylic acid anhydrides from alkenes without the need of individually synthesized or isolated C_{n+1} carboxylic acid co-substrates (Scheme 1c). We herein present a palladium-catalyzed synthesis of carboxylic

a. Hydrocarboxylation using formic acid



Scheme 1. a) Hydrocarboxylation of alkenes with formic acid to synthesize carboxylic acids (ref. [8]); b) Hydroacyloxycarbonylation of alkenes to synthesize carboxylic acid anhydrides (ref. [6]); c) Proposed concept of carbonylative synthesis of (symmetric) acid anhydrides from alkenes without the need of corresponding carboxylic acid.

acid anhydrides from alkenes with *in situ* produced carboxylic acids.

Results and Discussion

The reaction described herein is a tandem reaction as shown in Scheme 2 for styrene (1) as a model substrate. In the first step, a carboxylic acid (phenylpropionic acid, **2n** or **2b**) is formed from a reaction of **1** with CO and FA. In the second step, the produced carboxylic acid acts as the nucleophile in the carbonylation of **1**, forming the carboxylic acid anhydride (phenylpropionic acid anhydride, **3nn**, **3bn** or **3bb**). To analyze the reactant and products in this reaction, we implemented NMR analysis to quantify **2** (**2n**, **2b**) and **3** (**3nn**, **3bn**, **3bb**), and GC analysis to quantify **1**. The yield% was calculated with respect to the limiting reagent (in most cases formic acid unless otherwise specified).

Highly selective formation of linear acids or esters from alkenes can be achieved with a palladium-based catalytic system with the electron-rich and bulky ligand 1,2-bis(di-tertbutylphosphanylmethyl)benzene.^[9] However, in our previous studies on carbonylative synthesis of imides and acid anhydrides, we found that use of electron-donating ligands in this reaction resulted in very slow catalysis; the presence of relatively electron-withdrawing groups (such as phenyls) on phosphorus atoms appeared to be essential for achieving good yields.^[6,10] We also found that addition of strong acids is detrimental for catalysis, as most likely the presence of strong acid hampers formation of the carboxylate nucleophile. Based on this knowledge, for our initial trials in the current study we used the optimal conditions previously established for the carbonylation reaction of 1 with 3-phenylpropionic acid (2n): 1,4-bis(diphenylphosphanyl)butane (dppb) as the phosphine ligand in combination with Pd(OAc)₂ as the pre-catalyst in 1,2dichloroethane (DCE).

Ideally, the envisioned reaction should be carried out with an alkene to FA ratio of 2:1, as in the first step one equivalent of carboxylic acid **2** should be formed, which then acts as the nucleophile in the second step forming **3**. Thus, we started our investigations with a study to establish the optimal substrate to FA ratio, as we have shown in our previous work that the hydrocarbonylation of **1** with **2n** is an equilibrium reaction (with a calculated $\Delta G_{gas-phase}$ value close to zero), which benefits from the use of an excess of one of the substrates.



Scheme 2. Synthesis of acid anhydrides from styrene (1) and formic acid (FA): intermediates and products.

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We began with testing our established catalytic conditions for acid anhydride synthesis from alkenes with FA in excess (Table 1, entry 1). As expected, this resulted in ~90% phenylpropionic acid 2, (82:18 2n:2b), which confirmed the instability of the produced formate anhydride. An equimolar ratio of 1:FA resulted in the same yield of 2 with a trace amount of 3 nn (Table 1, entry 2). As decomposition of the formate anhydride to 2 is accompanied by the formation of CO, overall the net reaction does not consume CO, as is nicely demonstrated by the absence of a CO pressure drop (Figure S1). The result of this reaction seems to indicate faster kinetics of the nucleophilic attack by FA than by carboxylic acid 2, as hardly any anhydride 3 is formed. However, it cannot be excluded that upon formation of 3, a subsequent disproportionation reaction with FA ultimately results in generation of more 2.

Use of stoichiometric amounts (for the net desired reaction) of **1** and FA of 2:1 resulted in 70% yield of phenylpropionic anhydride (**3**) (Table 1, entry 3). This value is similar to the equilibrium yield reported in our previous work.^[6] Increasing the molar ratio of **1**:FA to 3:1 led to formation of **3** with a yield of 86% (Table 1, entry 4; please note that this yield is calculated with respect to the limiting reagent FA, the yield based on **1** is 57%). With the same amount of catalyst, the reaction could be scaled to 30:10 mmol 1:FA generating a yield of 88% **3** (Table 1, entry 5). Overall, we observe that the linearity obtained in both steps of the reactions is 75–80%, as reflected in the approximate 4:1 ratio found for **2n:2b**, and **3nn:3bn:3bb** ratios approaching the statistically expected values of 64:32:4.

We tested several phosphine ligands to study their influence on the reactivity and regioselectivity of the catalytic system (Table 2). A catalytic system comprising the tridentate ligand L1 did not yield any product. Use of L2 resulted in 82% yield of 3, whereas use of L3 resulted in a total anhydride yield of 72%, but at a higher reaction temperature of 85 °C. Catalytic systems



[a] Reaction conditions: CO (50 bar), Pd(OAc)₂ (0.05 mmol), dppb (0.10 mmol), DCE (6 mL), 70 °C, 15 h. Amount of products and regioselectivity of **2** and **3** determined by quantitative NMR analysis with dibromomethane as internal standard (error \pm 5%).

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[a] Reaction conditions: 1 (15.0 mmol), FA (5.0 mmol), CO (50 bar), Pd(OAc)₂ (0.05 mmol), ligand (0.10 mmol), DCE (6 mL), 70 °C, 20 h. Yield% (based on FA) and regioselectivity of 3 determined by NMR analysis with dibromomethane as internal standard. [b] 15 h instead of 20 h. [c] 85 °C instead of 70 °C. [d] 1 (7.5 mmol), FA (2.5 mmol), Pd(OAc)₂ (0.025 mmol), ligand (0.325 mmol).

comprising ligands with a rigid backbone, L4 and L5, were tested for their activity. Interestingly, use of the xylene-based ligand L4 resulted in 28% yield of 3 and 20% yield of 2 (Table 2, entry 5); apparently, the rigidity of the backbone significantly lowers the rate of the reaction. Similarly, the rate of the reaction using the catalytic system with L5 is even lower, yielding only 16% of 3 and 60% of 2, with a 2n:2b ratio of 66:34 (Table 2, entry 6). In conclusion, the tested ligands mostly affected the rate of the reactions. Use of the more rigid L4 or more electron-donating L5 resulted in low yields of anhydride 3 and build-up of intermediate 2. The linearity in products is approximately the same (75–80%) in all reactions with catalytic systems comprising phenyl-containing ligands, whereas use of L5 led to a lower linearity of about 65–70%.

Based on the commercial availability of the ligand dppb, and the fact that the different ligands result in more or less the same selectivity, a series of substrates were screened using the most active catalytic system dppb/Pd(OAc)₂ at an alkene:FA ratio of 3:1 and a catalyst loading of 1.0 mol% (Scheme 3). Since acid anhydrides are prone to degradation on isolation, the reaction mixtures were derivatized with pyrrolidine in basic conditions (unless specified otherwise, see Section S6) to produce amides; the amount of pure linear amide isolated by column chromatography is reported (provided yield% is related to FA as the limiting reagent, the numbers should be multiplied with 0.67 to obtain the yield% relative to alkene).

Linear amide 4n was isolated in 74% yield from our benchmark reaction with 1. The reaction can be applied to a large variety of styrene-based substrates, resulting in 5n-10n in moderate to high yields of 43-86%. In some of the reactions the NMR yield of the intermediate anhydride was significantly higher (Table S3), indicating that either the derivatization reaction or the isolation of the amide product is more difficult. The reaction with 2,4,6-trimethylstyrene as the substrate appeared to be significantly slower, as observed from the CO pressure drop (still dropping after a reaction time of 36 h), leading to a yield of 54% 7n on derivatization. The reaction with 3-CF₃-styrene resulted in 68% of anhydride, which was derivatized with (1R)-(+)-1-naphthylethylamine, providing **9n** in a yield of 58%. Compound 9n is an intermediate in the synthesis of the Cinacalcet,^[11] a drug used to treat hyperparathyroidism in patients on dialysis with chronic kidney disease. This result shows that our catalytic procedure has high potential to provide a sustainable synthetic route consisting of fewer steps.

Unactivated long-chain alkenes such as 1-octene and 1pentadecene yielded 93% 11n and 91% 12n, respectively. Cyclic alkenes are also efficiently converted into their corresponding amides, yielding 76% 13n and 81% 14n. The sterically demanding substrate (±)camphene yielded 39% of 15n (2:1 endo:exo) after a reaction time of 36 h. The CO pressure drop indicated that the catalysis was slow. Geminal disubstituted alkenes, a-methylstyrene and dihydrocarvone, yielded 62% 16n and 48% 17n (after 36 h), respectively. The catalytic system was found to be tolerant to functional groups such as ether (6n), ketone (17n), nitrile (18n), ester (19n), phosphinate ester (20) and silyl or silylether substituents (21 n, 22n), and gave modest (34% 22n) to excellent (84% 19n) yields. However, vinyl-based substrates containing a sulfone or phosphate group at the vicinal position generated little (< 10%) or no anhydride. Palladium black formation was observed in catalytic reactions with substrates containing silyl or silylether functional groups.

The reactions in this substrate scope were carried out using an excess of alkene (alkene:FA of 3:1), in order to drive the equilibrium to completion. However, whereas FA is readily available, very often the substrate alkenes are expensive or obtained after a multi-step synthetic route and hence, a 2:1 alkene:FA substrate ratio would seem practical. Testing the substrate ratio 2:1 alkene:FA on alkene substrates 1-octene, cyclopentene, allyl cyanide and trimethylvinylsilane resulted in 82, 59, 58 and 37% yield of total anhydride as compared to 67, 51, 48 and 29% (yield% with respect to alkene) respectively when 3:1 alkene:FA was used.

Furthermore, the catalytic procedure was applied to an estrone derivative (scale: 2:1 mmol). For this reaction a catalyst loading of 2.5 mol% was used in order to obtain a reasonable

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Scheme 3. Substrate Scope. Reaction conditions: alkene (3.0 equiv.; 15 or 7.5 mmol), FA (1.0 equiv.; 5 or 2.5 mmol), CO (50 bar), Pd(OAc)₂ (1.0 mol%), dppb (2.0 mol%), DCE (6.0 mL), 70 °C, 20 h. [a] 15 h instead of 20 h. [b] 36 h instead of 20 h. [c] alkene (3.0 equiv.; 30 mmol), FA (1.0 equiv.; 10 mmol), CO (50 bar), Pd(OAc)₂ (0.5 mol%), dppb (1.0 mol%), DCE (6.0 mL), 70 °C, 24 h. [d] presence of branched product, ratio of l:b = 79:21. [e] alkene (2.0 mmol), FA (1.0 mmol), CO (50 bar), Pd(OAc)₂ (2.5 mol%), dppb (5.0 mol%), DCE (6.0 mL), 70 °C, 20 h. Yield% are based on FA. Synthetic Applications. One-pot derivatizations of catalytic reaction mixtures to synthesis amide, ester, thioester and ketones. [f] presence of branched product, l:b = 79:21. [g] presence of branched product, l:b = 85:15. [h] presence of branched product, l:b = 92:8. Yield% is based on FA.

rate for this dilute reaction, and 74% benzylamide **25 n** was attained on derivatization with benzylamine.

The reactivity of acid anhydrides allows access to molecules that may be otherwise difficult to obtain *via* classical hydro-

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carbonylation reactions, due to either low reactivity of the nucleophile or poisoning of the catalyst by the nucleophile. The synthesis of primary amides using ammonia as nucleophile in carbonylation reactions is challenging, related to the basicity of ammonia hampering metal-hydride formation, and deactivation of the metal catalyst by formation of unreactive ammine complexes.^[12] With our catalytic procedure generating intermediate anhydrides from alkenes and FA, a one-pot derivatization with ammonia resulted in 83% of the primary amide 26 in 79% linearity. Poorly nucleophilic alcohols such as β-naphthol reacted with our catalytic mixture to form ester 27 n in a yield of 74%. Thiols, which are often considered as poisons in palladium-mediated catalysis, can be used as nucleophiles to produce thioesters,^[13] and indeed derivatization of a reaction mixture with tert-butylthiol resulted in 92% thioester 28 with 85% linear selectivity. Finally, we were able to generate ketones in excellent yields via a Friedel-Crafts acylation with anisole (97%, 29n), or a metal-catalyzed Suzuki coupling with phenylboronic acid (84%, 30).

The carbonylation reaction with carboxylic acids as the nucleophiles most likely proceeds via the classical palladiumhydride mechanism^[14] for the two cycles, first with FA as the nucleophile forming the formate anhydride that decomposes to a carboxylic acid, which then acts as the nucleophile in the second reaction (Scheme 4). Thus, in the first cycle acylpalladium species I undergoes a nucleophilic attack by FA to form a formate-mixed anhydride via intermediate IIa. This formate acid anhydride is unstable at higher temperatures, decomposing to release CO and carboxylic acid. The CO released in this case compensates for the CO consumed and hence, we do not observe a drop in CO pressure when we use equimolar amounts of 1:FA to form 2 (see Figure S1). The formed carboxylic acid may then act as a nucleophile reacting with I to form intermediate IIb, which yields the acid anhydride fully derived from two molecules of the alkene.



Scheme 4. Postulated mechanism of tandem hydroacyloxycarbonylation of alkenes to synthesize acid anhydrides.

Conclusions

In summary, a carbonylative synthesis is reported for the production of carboxylic acid anhydrides from alkenes via a tandem reaction using FA for in situ generation of a carboxylic acid. The catalytic procedure is applicable to a wide range of substrates and is tolerant to various functional groups, producing moderate to excellent yields of acid anhydrides derived from two molecules of the alkene substrate. Furthermore, the acid anhydrides formed can be derivatized to amides, esters, thioesters and ketones by simple one-pot derivatization reactions. Using our procedure, the formation of symmetric acid anhydrides from alkenes comes within reach, if a catalytic system can be developed that exhibits high regioselectivity. Moreover, a recent report on formation of two molecules of acyl derivative, instead of one, by electrophilic activation of symmetric acid anhydrides^[15] further adds to the future scope for sustainability of this reaction.

Experimental Section

Palladium acetate (1.0 mol %)1.4and bis(diphenylphosphanyl)butane, dppb, (2.0 mol%) were weighed into a clean and dried glass liner containing an oven-dried stirring bar. The glass liner was fitted inside a 100 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. A freeze-pump-thawed solution of formic acid (1.0 equiv.) in dried DCE (6.0 mL) was added using standard Schlenk techniques and the mixture was stirred for 30 mins. Then the required volume of degassed and dried alkene (3.0 equiv.) was added using standard Schlenk procedures and the autoclave was closed and disconnected from the Schlenk line. The autoclave was transferred to a HEL PB4 polyblock and connected to the gas lines. The lines connecting the autoclave was flushed with nitrogen (N_2) (3×30 bar). The autoclave was flushed with carbon monoxide (CO) (1×30 bar) and then was charged with CO to 50 bar. The autoclave was stirred at 350 rpm and heated for 20 to 36 h at 70 °C. At the end of the reaction time, the autoclave was brought to room temperature, cooled further for 30 minutes using an ice-bath and then was slowly depressurized. After 30 minutes of thawing, the contents of the glass liner were transferred to a 10 mL volumetric flask and the total volume was adjusted to 10 mL using dichloromethane (DCM). The reaction mixture was analyzed using GC and NMR techniques. Additionally, the catalytic reaction mixture was subjected to derivatization for amide formation.

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Conflict of Interests

The authors declare no conflict of interest.



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The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbonylation \cdot alkene \cdot formic acid \cdot carboxylic acid anhydride \cdot palladium catalysis

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