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Pd-Catalyzed Selective Carbonylation of *gem*-Difluoroalkenes: A Practical Synthesis of Difluoromethylated Esters

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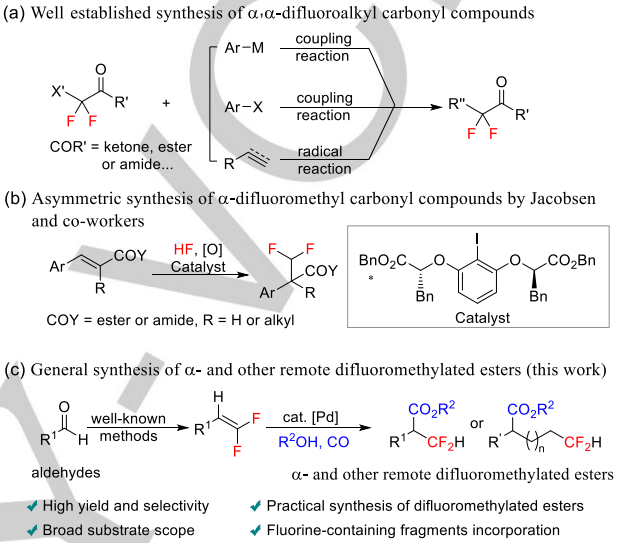
Abstract: The first catalyst for the alkoxycarbonylation of *gem*-difluoroalkenes is described. This novel catalytic transformation proceeds in the presence of $Pd(acac)_2$/1,2-bis((di-*tert*-butylphosphan-yl)methyl)benzene (btbpx) (**L4**) and allows for an efficient and straightforward access to a range of difluoromethylated esters in high yields and regioselectivities. The synthetic utility of the protocol is showcased in the practical synthesis of a Cyclandelate analogue using this methodology as the key step.

The incorporation of fluorine or fluorinated building blocks into organic molecules has become an important tool for designing bioactive compounds and to improve the properties of functional materials.[1] Thus, in recent years the controlled introduction of these groups represents one of the most active areas in the development of novel synthetic methodologies.[2]

Among the various fluorinated moieties, the difluoromethyl group (CF_2H) is a particularly interesting one. Compared with the well-known CF_3 substituent, this group bears a slightly acidic C-H bond,[3] which is capable of hydrogen-bonding interactions to improve the binding selectivity to specific receptors.[4] Moreover, the difluoromethyl group is recognized as being isosteric and isopolar with alcohols[5] or thiols.[6] Thus, at present there is a strong interest to replace hydroxyl, amino, or thio substituents by CF_2H groups within lead structures of pharmaceuticals.[7] Although significant advancements have been made in the direct introduction of CF_2H group into organic compounds,[8] including electrophilic, [9] nucleophilic, [10] free-radical, [11] and difluorocarbene-involving[12] reactions, the preparation of functionalized difluoromethyl and α,α-difluoroalkyl carbonyl compounds is still highly desired.

Today, transition metal catalyzed cross-coupling reactions using commercially available $BrCF_2CO_2Et$ or its analogs with organometallic regents[13] and the radical-induced functionalization of alkenes and/or alkynes[14] provide the most convenient strategies for the synthesis of α,α-difluoroalkyl carboxylic acid derivatives (**Scheme 1**, a).[15] Nevertheless, for the preparation of α-difluoromethyl compounds, few efficient catalytic reports exist.[16] Notably, in 2016 Jacobsen and co-workers developed the first catalytic asymmetric geminal difluorination of β-substituted styrenes to give difluoromethylated carbonyl compounds with tertiary or quaternary stereocenters (**Scheme 1**, b).[17] We thought a complementary practical approach to this interesting class of products can be achieved by carbonylation of *gem*-difluoroalkenes (**Scheme 1**, c).



Scheme 1. Synthesis of α,α-Difluoroalkyl Carbonyl Compounds and α-Difluoromethyl Carbonyl Compounds.

As one of the most important processes for producing carboxylic derivatives, transition metal catalyzed carbonylation reactions have been extensively investigated and applied in academia and industry for several decades.[18] In this respect, the alkoxycarbonylation represents a well-established method for the transformation of alkenes into the corresponding esters.[19] In recent years, notable advancements were achieved with respect to catalyst activity,[20] selectivity,[21] and CO surrogates.[22] To the best of our knowledge, the direct alkoxycarbonylation of such functionalized olefins to give difluoromethylated esters has not been reported yet. Obviously, a key challenge for such process is to avoid the competitive β-F elimination to form undesired byproducts.[23] Advantageously, there are many methods and reagents developed for the synthesis of *gem*-difluoroalkenes from aldehydes and ketones.[24]

Based on our continuous interest in carbonylations, herein we present the first examples of alkoxycarbonylations to construct α-difluoromethylated esters. Interestingly, using aliphatic alkenes a cascade isomerization-alkoxycarbonylation allows for remote olefin functionalization in high yield and selectivity.

Recently, we demonstrated the advantage of specific phosphine ligands with built-in-base function for Pd-catalyzed alkoxycarbonylations of less-reactive olefins including hindered tetra-substituted alkenes.[20] Incorporation of *tert*-butyl and pyridine substituents on the phosphorous atom of several bidentate phosphine ligands dramatically improved the rate of the nucleophilic attack on the intermediate Pd acyl complex, which can be rate-limiting step in these catalytic protocols. [25] Hence, at the start of our studies, we investigated the influence

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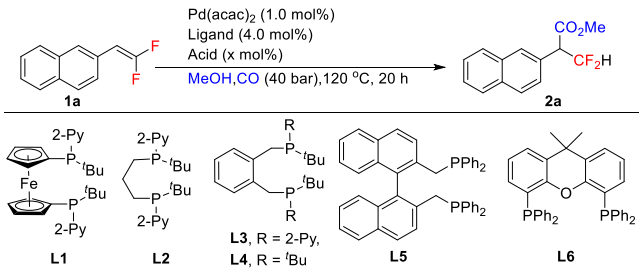
of these and related standard ligands for the methoxycarbonylation of 2-(2,2-difluorovinyl)naphthalene **1a** under typical carbonylation conditions for alkenes (Table 1).

Table 1. Pd-Catalyzed Alkoxcarbonylation of 2-(2,2-Difluorovinyl)naphthalene: Investigation of Reaction Conditions[a]



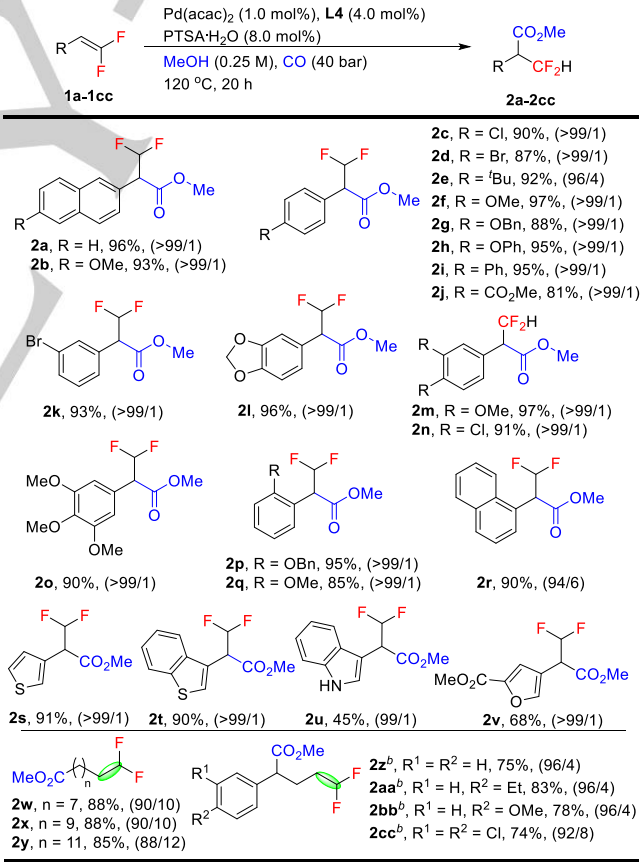
Entry	Ligand	Acid (x)	*b*/*l*[b]	Yield (%)[b]
1	**L1**	PTSA·H_2O (16)	98/2	18
2	**L2**	PTSA·H_2O (16)	76/24	7
3	**L3**	PTSA·H_2O (16)	93/7	72
4	**L4**	PTSA·H_2O (16)	>99/1	92
5	**L5**	PTSA·H_2O (16)	93/7	5
6	**L6**	PTSA·H_2O (16)	>99/1	9
7	**L4**	No acid	-/-	0
8	**L4**	HOAc (16)	-/-	0
9	**L4**	H_2SO_4 (8)	92/8	5
10	**L4**	HOTf (16)	>99/1	91
11	**L4**	**PTSA·H_2O (8)**	**>99/1**	**97 (96[c])**
12	**L4**	PTSA·H_2O (5)	>99/1	93

[a] Reaction conditions: **1a** (0.5 mmol), $Pd(acac)_2$ (1.0 mol%), **L** (4.0 mol%) PTSA·H_2O (16.0 mol%), CO (40 atm),120 °C and methanol (2.0 mL). [b] The ratio of branched/linear (*b*/*l*) and yield was determined by GC. [c] Isolated yield.

Applying 1,1'-ferrocenediyl-bis(*tert*-butyl(pyridin-2-yl)phosphine) **L1**, ester **2a** was obtained with excellent regioselectivity albeit in 18% yield. In the presence of 1,3-bis(*tert*-butyl(pyridin-2-yl)phosphanyl)propane **L2** as the ligand, the yield of the desired product was even lower. To our delight, using 1,2-bis((*tert*-butyl(pyridin-2-yl)phosphanyl)methyl)benzene **L3** the desired product **2a** was obtained in 72% yield. Surprisingly, the commercially available 1,2-bis((di-*tert*-butylphosphanyl)methyl)benzene (btbpx) ligand **L4**[26] which has the same backbone to **L3**, gave an improved yield of 92% and >99/1 regioselecivity. Other commonly used bidentate phosphine ligands such as Naphos **L5** and Xantphos **L6** only afforded the product in poor yields. No reaction occurred without acid or weak acid. Even sulfuric acid gave only trace amounts of **2a**, while trifluoromethanesulfonic acid afforded the desired product in 91 % yield with excellent regioselectivity. Besides, the acid concentration had a significant influence on the productivity giving **2a** in 93% and 97% in the presence of 5 and 8 mol% PTSA, respectively.

With optimized reaction conditions established, we examined the substrate scope of this process. First, we studied the alkoxycarbonylations of different *gem*-difluoroalkenes, a variety of aromatic *gem*-difluoroalkenes bearing diverse substituents and heterocycles, are transformed into the corresponding products in high yields with excellent regioselectivities. More specifically, *gem*-difluoroalkenes **1a**–**k** with either electron-donating (OMe, OBn, OPh) or electron-withdrawing (Cl, Br, CO_2Me) groups on the phenyl ring provided the corresponding products **2a**–**k** in 85-98%. Notably, in case of bromo-substituted substrates, which provide useful handles for further synthetic transformations, no dehalogenation was observed. Furthermore, substrates **1l**-**1o** with multiple functional groups, also give the corresponding products **2l**-**2o** in 90-97%. The position of substituents on the phenyl ring has no influence on the reaction outcome. Hence, *gem*-difluoroalkenes **1p**-**1r** afforded **2p**-**2r** in very good yields and selectivities. Interestingly, heterocycle-substituted *gem*-difluoroalkenes based on (benzo)thiophene, indole and furan proved to be viable substrates and gave the corresponding products **2s**-**2v** in moderate to excellent yields. It should be noted that the product **2u** was obtained by carbonylation and deprotection of 1-(3-(2,2-difluorovinyl)-1H-indol-1-yl)ethan-1-one under standard conditions. Unfortunately, when other heterocyclic including 2-(2,2-difluorovinyl)benzofuran, quinoline as well as *tetra*-substituted difluoroalkenes were used, no desired product was detected (see SI, Table *S*8 and *S*11).

Table 2. Substrate Scope with Respect to *gem*-Difluoroalkenes[a]

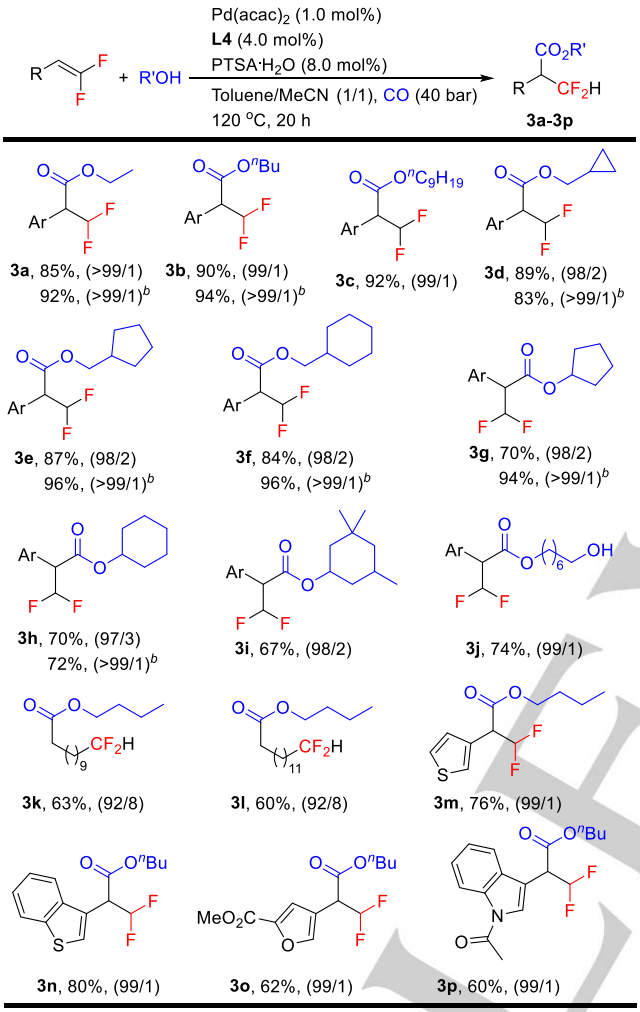


[a] Reaction conditions: **1** (0.5 mmol), $Pd(acac)_2$ (1.0 mol%), **L4** (4.0 mol%) PTSA·H_2O (16.0 mol%), CO (40 atm),120 °C in methanol (2.0 mL). Isolated yield for all products. The ratio of branched/linear was determined by GC. [b] 3/12/12 mol% of Pd/**L4**/PTSA·H_2O and CO (50 atm).

Next, we evaluated the reactivity of aliphatic *gem*-difluoroalkenes, which from the viewpoint of selectivity represent more demanding substrates as they may undergo additional isomerization reactions. Nevertheless, alkoxycarbonylations proceeded selectively to afford various difluoromethylated esters.

The linear long chain aliphatic substrates **1w**, **1x** and **1y** without other functional groups gave the corresponding products **2w**-**2y** in good to high yields and selectivities. The isomerization process for those substrates takes place at a faster rate than the carbonylation in α-position explaining the selectivity towards the linear ω-ester. Reactions of 1,1-difluoro-4-arylbutenes **1z**-**1cc** also reacted well leading to the γ-difluoromethylated esters **2z**-**2cc** in good to high yields and selectivities, albeit at higher catalyst loading and higher CO pressure.

Table 3. Substrate Scope with Respect to Alcohols[a]

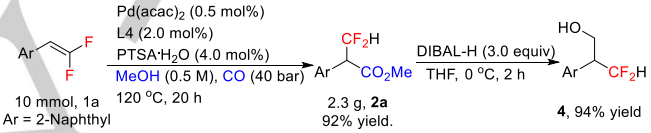


[a] Reaction conditions: **1** (0.5 mmol), ROH (1.5 mmol), $Pd(acac)_2$ (1.0 mol%), **L4** (4.0 mol%) $PTSA{\cdot}H_2O$ (16.0 mol%), CO (40 atm),120 °C in toluene/MeCN (1/1). Isolated yield for all products. The ratio of branched/linear was determined by GC. For **3a**-**3j**, Ar = 2-Naphthyl. [b] 1.0 mL alcohols were used as solvents.

To demonstrate that this novel transformation can be applied to wider scope of alcohols, we investigated the alkoxycarbonylation of **1a** with *n*-butanol as the nucleophile. Hence, different solvents and conditions were tested using **L4** as the ligand, and the yield and selectivity was optimized to be 94% and 99/1 when a mixed solvent system of toluene and acetonitrile (v/v = 1/1) was used (see SI for more details).

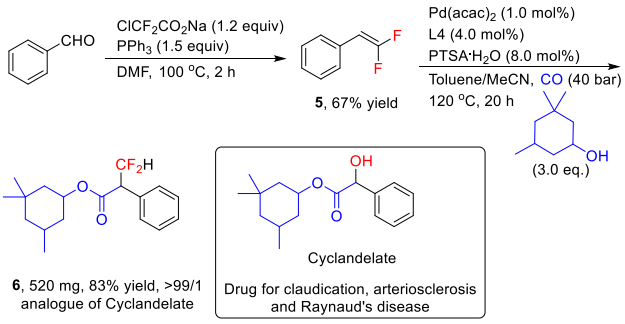
Under this optimized conditions, the scope of different alcohols with 2-(2,2-difluorovinyl)naphthalene **1a** were examined (Table 3). Gratifyingly, the corresponding esters were obtained in good to high yields, again with excellent regioselectivities. For example, primary alcohols, such as ethanol, *n*-butanol, *n*-nonanol, cyclopropylmethanol, cyclopentylmethanol, and cyclohexylmethanol, gave the desired products **3a-3f** in 84-92% yield. Similarly, carbonylations with less reactive secondary alcohols, for instance cyclopentanol, cyclohexanol and *cis*-3,3,5-trimethylcyclohexanol proceeded smoothly, providing the products **3g**-**3i** in 67-94% yield. Moreover, 1,7-heptanediol could also be used in this reaction to afford selectively the monoester product **3j**. Notably, in case of inexpensive alcohols (see products **3a**, **3b** and **3d**-**3h**) the reactions can be easily performed in neat alcohol. Furthermore, aliphatic and heterocyclic *gem*-difluoroalkenes also gave the corresponding products **3k**-**3p** in 60-80% yield.

A practical advantage of the presented methodology is the possibility for easy scale up. Hence, we performed the gram-scale synthesis of **2a** under 0.5 mol% Pd catalysts loading and the desired product was obtained in 92% yield (Scheme 2). Obviously, this and related esters present versatile building blocks which can be straightforwardly converted to interesting amides, acids, nitriles, alcohols, and so on. To showcase such possibilities, the reduction of **2a** to **4** has been performed. To explore the stability of the system, we further decreased the catalyst loading. Keeping the acid concentration constant and fixing the **L4** concentration to 2 mmol/L, at **1a**/Pd ratio >10000, TONs up to 8400 were reached (for more details, see Table S9).



Scheme 2. Gram-Scale Synthesis of **2a**

To highlight the usefulness of our protocol further on, we synthesized the analogue of Cyclandelate, which is a commonly used drug for claudication, arteriosclerosis and Raynaud's disease. The desired product **6** was achieved in 83% yield via direct alkoxycarbonylation of *gem*-difluoroalkene **5** with 3,3,5-trimethylcyclohexanol under the optimized reaction conditions. To the best of our knowledge, this is the first example for the synthesis of this drug's analogue.



Scheme 3. Practical Synthesis of Cyclandelate Analogue

In summary, we have developed the first selective carbonylation of *gem*-difluoroalkenes. This catalytic protocol makes use of a Pd/**L4** catalyst and provides a variety of synthetically useful difluoromethylated esters in high yields and excellent regioselectivities. Due to availability of starting materials and the step-economy, this procedure is efficient and easy to scale up. The straightforward synthesis of a Cyclandelate analogue demonstrates the synthetic utility of this methodology. It is expected to provide other valuable difluoromethyl-containing building blocks for modern organic synthesis and complements the currently known carbonylation methods.

Acknowledgements

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Keywords: carbonylation • fluoroalkenes • difluoromethylated esters • palladium• selectivity

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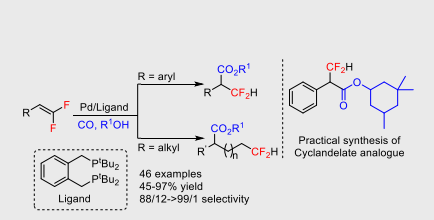

The first selective carbonylations of gem-difluoroalkenes was developed, providing a general approach to a variety of synthetically useful difluoromethylated esters in high yields and excellent regioselectivities.

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Pd-Catalyzed Selective Carbonylation of gem-Difluoroalkenes: A Practical Synthesis of Difluoromethylated Esters