

An Efficient and Practical Sequential One-Pot Synthesis of Suprofen, Ketoprofen and Other 2-Arylpropionic Acids

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Received: July 4, 2008; Published online: October 7, 2008

Abstract: A novel sequential double carbonylation to synthesize anti-inflammatory drugs such as Ketoprofen and Suprofen has been developed. Starting from easily available aryl halides and arylboronic acids a one-pot carbonylative Suzuki and hydroxycarbonylation reaction sequence proceeds in good selectivity and high yield in the presence of the palladium/cataCXium[®] A catalyst system. Applying optimized conditions different 2-arylpropionic acids were synthesized in good yields.

Keywords: homogeneous catalysis; hydroxycarbonylation; palladium; profenes; Suzuki carbonylation

Introduction

2-Arylpropionic acids constitute an important class of non-steroidal anti-inflammatory drugs (NSAID) and analgesic agents.^[1] Ibuprofen, the prototype of the 2-arylpropionic acid family, was developed already in 1965 by Stuarts. Since then, a number of structurally related drugs such as Naproxen, Ketoprofen, and Suprofen have been established and are used for the treatment of diverse diseases.

Among the various methods developed for the synthesis of 2-arylpropionic acids,^[2] the acid-mediated and palladium-catalyzed hydroxycarbonylation of vinylarenes constitutes a straightforward and general approach towards profenes. Due to the commercial and pharmaceutical importance of these drugs, several

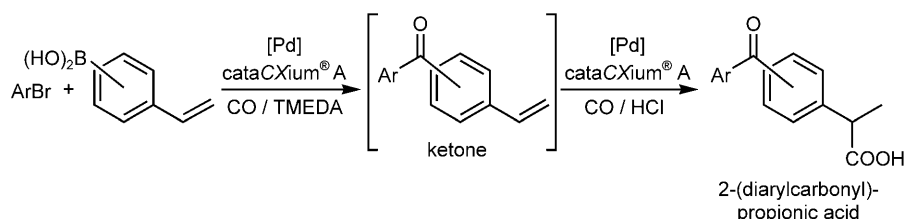
papers and patents have been published on this subject. The range of known catalyst systems varies from simple Pd(OAc)₂-LiCl-TsOH^[3], [Pd]-CuCl₂-H⁺ in the presence of O₂^[4] and phosphine ligands^[5], Pd(OAc)₂ in the presence of mono- or diphosphines and oxalic acid,^[6] to water-soluble Pd complexes containing trisulfonated triphenylphosphine.^[7]

Recently, we developed a novel synthetic protocol for the preparation of diaryl ketones *via* carbonylative Suzuki coupling in the presence of Pd(OAc)₂/cataCXium[®] A.^[8] More specifically, we demonstrated that, at a low pressure of carbon monoxide, even vinyl-substituted diaryl ketones are formed in high yield starting from vinyl-substituted arylboronic acids and aryl bromides. Based on this methodology, we had the idea to combine carbonylative Suzuki reactions with a palladium-catalyzed hydroxycarbonylation (Scheme 1).

Such a one-pot protocol would circumvent the laborious industrial multi-step procedure for Ketoprofen^[9] and Suprofen^[10]. Here, we describe an efficient process for palladium-catalyzed sequential carbonylations towards various aryl propionic acids, e.g., Ketoprofen and Suprofen. We believe our protocol constitutes the shortest route to this type of profenes.

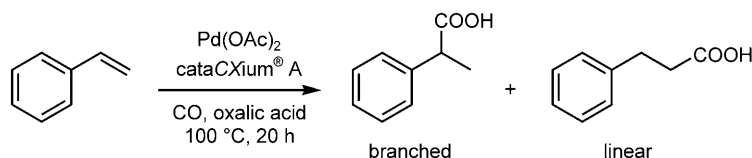
Results and Discussion

Initially, the palladium-catalyzed hydroxycarbonylation of styrene was studied as a model system. Since palladium/cataCXium[®] A has been proven to be optimal for the carbonylative Suzuki reaction, we started



Scheme 1. A novel approach towards arylpropionic acids.

Table 1. Hydroxycarbonylation of styrene: Screening of reaction parameters.^[a]



Entry	Pd(OAc) ₂ [mol%]	CataCXium® A [mol%]	Solvent	CO [bar]	Conversion ^[b] [%]	Branched ^[c] [%]	Linear ^[c] [%]
1	0.75	4.5	DME	30	49	24	3
2	0.75	4.5	DME	5	31	3	0
3	0.75	4.5	dioxane	30	76	68	1
4	0.75	4.5	dioxane	10	57	40	2
5	0.75	4.5	dioxane	40	87	78	0
6	0.75	4.5	dioxane	50	83	76	0
7	0.50	1.5	dioxane	40	50	42	0
8	0.50	2.0	dioxane	40	64	56	0
9	0.50	3.0	dioxane	40	76	69	0
10 ^[d]	0.75	4.5	dioxane	40	98	67	0
11 ^[e]	0.75	4.5	dioxane	40	80	74	0

^[a] Reaction conditions: 1 mmol styrene, 1 equiv. of oxalic acid, 0.5–0.75 mol% Pd(OAc)₂, 1.5–4.5 mol% cataCXium® A, 2 mL solvent, 0.2 equiv. of hexadecane (internal standard), 5–50 bar CO, 100 °C, 20 h.

^[b] Reaction mixture was used to determine the conversion by GC.

^[c] A sample was esterified with MeOH and trimethylsilyldiazomethane to determine the yield by GC.

^[d] Addition of 2 equiv. of H₂O.

^[e] Addition of 2 equiv. of MeOH gave only 9% yield without esterification with trimethylsilyldiazomethane.

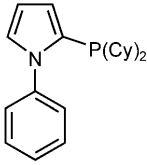
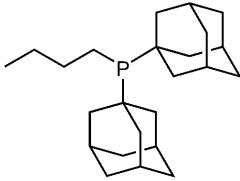
investigating this catalyst system.^[11] Based on the results of Alper et al. and van Leeuwen et al.^[6], we decided to examine the carbonylation reaction in the presence of oxalic acid (Table 1). Applying 0.75 mol% Pd(OAc)₂/4.5 mol% cataCXium® A and one equiv. of oxalic acid, we obtained 24% of the desired branched 2-arylpropionic acid and 3% of the linear regioisomer in DME at 30 bar CO and 100 °C (Table 1, entry 1). When the CO pressure was reduced to 5 bar, the yield dropped to 3% (Table 1, entry 2). Advantageously, the yield was significantly improved by using dioxane as solvent. Thus, we obtained 68% of the desired product with >98% regioselectivity at 30 bar CO and 100 °C (Table 1, entry 3). Addition of two equiv. of H₂O did not change the yield (Table 1, entry 10). However, adding two equiv. of MeOH slightly increased the yield up to 74% (Table 1, entry 11). The optimum of yield was found at 40–50 bar CO (76–78%, Table 1, entries 5 and 6). Even in the presence of 0.5 mol% Pd(OAc)₂ 69% of the desired product was obtained (Table 1, entry 9). Next, we tested the influence of different ligands and acids in our optimized hydroxycarbonylation reaction (Table 2). Monodentate ligands such as cataCXium PCy₂, PPh₃ and PCy₃ showed high regioselectivity, but the yield decreased to 30–58% (Table 2, entries 1, 3, and 5). In accordance with the results of van Leeuwen, we observed for the bidentate ligands DPPP and DPPF a shift towards the linear product, although the yield was low under these conditions

(13–24%, Table 2, entries 7 and 9). In contrast to the reactions with oxalic acid, the use of 37% HCl resulted in higher yield and full conversion since chloride ions are known to promote the hydroxycarbonylation.^[5b] In the case of cataCXium PCy₂ and PPh₃ the product was observed in 77% and 54%, respectively (Table 2, entries 2 and 4). CataCXium® A even furnished 94% of the branched acid (Table 2, entry 11)! On the other hand, only low yield (0–5%) was achieved in the presence of PCy₃ and the chelating ligands DPPP and DPPF (Table 2, entries 6, 8 and 10). Using either *p*-TSA or formic acid in the presence of cataCXium® A caused lower conversion (32–37%) and yield (7–10%, Table 2, entries 12 and 13).

Applying the optimized conditions, Suprofen and Ketoprofen were synthesized in good to excellent yield (80 and 99%) from thiophen-2-yl 4-vinylphenyl ketone and phenyl 3-vinylphenyl ketone, respectively (Scheme 2). The starting material is obtained by Suzuki carbonylation of the corresponding aryl bromide and vinylboronic acids according to our previous protocol.^[8] Since both single carbonylation reactions proceeded with high yield and selectivity in the presence of the same type of catalyst, we studied the possibility to run both reactions without any isolation of intermediates in one pot.

The conditions for the first step were adopted from the synthetic protocol for the Suzuki carbonylation. Instead of one equiv. of TMEDA, 0.75 equiv. of base were used. This reduced amount of TMEDA did not

Table 2. Hydroxycarbonylation of styrene: different ligands and acids.^[a]

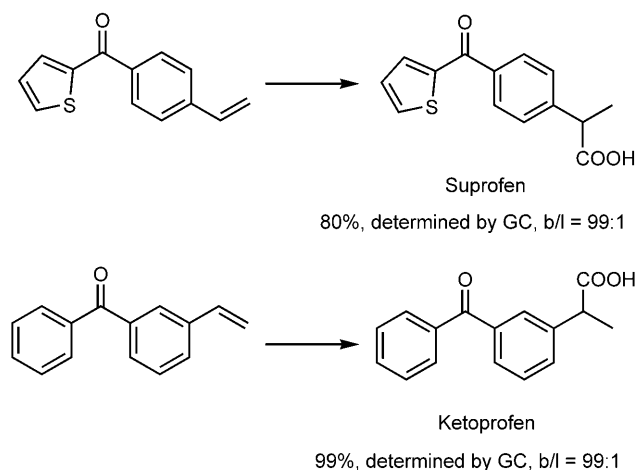
Entry	Ligand	Acid	Conversion ^[b] [%]	Branched ^[c] [%]	Linear ^[c] [%]
1		oxalic acid	36	30	0
2		37% HCl	100	77	0
	cataCXium PCy ₂				
3	PPh ₃	oxalic acid	37	30	0
4		37% HCl	100	54	2
5	PCy ₃	oxalic acid	59	58	1
6		37% HCl	100	0	0
7	dppp	oxalic acid	56	2	13
8		37% HCl	100	4	0
9	dppf	oxalic acid	48	11	24
10		37% HCl	100	5	0
11		37% HCl	100	94	0
12		<i>p</i> -TSA	37	10	1
13		98% formic acid	32	7	1
	cataCXium® A				

^[a] Reaction conditions: 1 mmol styrene, 1 mmol acid, 0.75 mol% Pd(OAc)₂, 4.5 mol% of monodendate or 2.25 mol% of bidentate ligand, 2 mL of dioxane, 0.2 mmol hexadecane (internal standard), 40 bar CO, 100 °C, 20 h.

^[b] Reaction mixture was used to determine the conversion by GC.

^[c] A sample was esterified with MeOH and trimethylsilyldiazomethane.

decrease the yield and should avoid an inhibition of the hydroxycarbonylation, which proceeds under acid conditions. After Suzuki carbonylation, one equiv. of



Reaction conditions: 1 mmol vinyl aryl ketone, 1 mmol 37% HCl, 0.75 mol% Pd(OAc)₂, 4.5 mol% cataCXium® A, 2 mL dioxane, 0.4 mmol hexadecane (internal standard), 40 bar CO, 100 °C, 20 h.

Scheme 2. Synthesis of Suprofen and Ketoprofen.

37% HCl in dioxane was added to the reaction mixture, which started the hydroxycarbonylation process. The results of the sequential double carbonylation process are summarized in Table 3. To our delight, the hydroxycarbonylation was not hampered and provided Suprofen (72%) and Ketoprofen (93%) with excellent selectivity (Table 3, entries 1 and 2). Our novel double carbonylation protocol was further successfully extended to other aryl bromides containing both electron-donating and electron-withdrawing substituents. Starting from 4-bromoanisole, 71% of the desired product was observed in the hydroxycarbonylation step and 45% over-all yield is achieved after esterification (Table 3, entry 3). 4-Trifluorobromobenzene provided 95% of product in the hydroxycarbonylation step and 70% isolated over-all yield after esterification (Table 3, entry 4). Finally, to demonstrate the feasibility of our approach on a larger scale we synthesized Ketoprofen on a 51-g scale with an over-all yield of 74%.

Conclusions

In conclusion, we have developed a novel synthetic protocol for pharmaceutically important profenes,

Table 3. One-pot Suzuki carbonylation-hydroxycarbonylation sequence.

Entry	Ketone ^[a]	Con- version [%]	Yield [%]	2-(Diarylcarbonyl)-propionic acid ^[b]	Con- version ^[c] [%]	Branched ^[d] [%]	Linear ^[d] [%]	Yield ^[e] [%]
1		100	97		98	72	2	68
2		81	70		100	93	2	60
3		100	68		100	71	8	45
4		100	78		95	95	2	70

^[a] Reaction conditions: 10 mmol ArBr, 15 mmol vinyl boronic acid, 7.5 mmol TMEDA, 0.75 mol% Pd(OAc)₂, 4.5 mol% cataCXium® A, 10 mL toluene, 2 mmol hexadecane (internal standard), 2.5 bar CO, 80 °C, 24 h; in the case of 4-bromoanisole a temperature of 100 °C was required.

^[b] Reaction conditions: 15 mL dioxane, 10 mmol 37% HCl, 40 bar CO, 100 °C, 20 h.

^[c] Reaction mixture was used to determine the conversion.

^[d] A sample was esterified with MeOH and trimethylsilyldiazomethane to determine the yield by GC.

^[e] Isolated over-all yield of branched methyl ester.

which includes two different catalytic carbonylation reactions. Both the Suzuki carbonylation and the hydroxycarbonylation are catalyzed by the same catalyst system [Pd(OAc)₂/cataCXium® A] and can be carried out efficiently in one pot.

Experimental Section

All reactions were carried out under an argon atmosphere using Schlenk techniques. DME and dioxane were distilled from calcium hydride under argon. Toluene was distilled from sodium and benzophenone ketyl. Chemicals were purchased from Aldrich, Fluka and Strem and were used without further purification. CataCXium® A was provided by Evonik Industries. *m*-Vinylbenzeneboronic acid^[12] was synthesized from *m*-bromostyrene^[13] which was obtained from

commercially available 3-bromo- α -methylbenzyl alcohol. Column chromatography was performed on Silica gel 60 (230–400 mesh). Gas chromatography was done on a Hewlett Packard HP 6890 chromatograph with a HP5 column. NMR data were obtained from a Bruker ARX 300. ¹H and ¹³C NMR spectra are referenced to the residual solvent signals. IR spectra of compounds were recorded using ATR method on a Nicolet Magna 550. Mass spectroscopy was performed on a 5973 Network Mass Selective Detector from Agilent Technologies. Elemental analyses were determined using a TruSpec® micro analyser from Leco.

Experimental Procedure for the Ligand and Acid Screening

The reaction was carried out in a 300-mL autoclave from the 4560 series of Parr Instruments®. The autoclave contained an alloy plate to hold six 4-mL glass vials. The vials

were charged with 4.5×10^{-2} mmol (4.5 mol%) monodentate ligand or with 2.25×10^{-2} mmol (2.25 mol%) bidentate ligand and a magnetic stirring bar. The vials were closed *via* septums containing an inlet needle and were flushed with argon. When solid acids were used, 1 mmol *p*-TSA or 1 mmol oxalic acid were added to the vials. 2.17 mL of stock solution containing styrene (1.15 mL, 10 mmol), Pd(OAc)₂ (16.8 mg, 0.075 mmol), hexadecane (590 μ L, 2 mmol) and 20 mL of dioxane were added to each vial by syringe. Subsequently, in the case of liquid acids 1 mmol of 37% HCl or 1 mmol of 98% formic acid was added to the solution. Then, the alloy plate was transferred into the autoclave. The sealed autoclave was purged with CO several times and pressurized with 5–50 bar CO at room temperature. Afterwards, it was heated to 100 °C and the reaction was run for 20 h at this temperature. In order to determine the yield by GC, a sample of 100 μ L of each reaction solution was esterified with trimethylsilyldiazomethane in the presence of 100 μ L MeOH. Since trimethylsilyldiazomethane reacts sometimes with vinylarenes, a sample of the reaction solution with one aliquot of MeOH was taken without addition of trimethylsilyldiazomethane to determine the conversion by GC.

Experimental Procedure for the Sequential Double Carbonylation in One Pot

A 100-mL Schlenk flask was charged with Pd(OAc)₂ (16.8 mg, 0.075 mmol), cataCXium® A (161.3 mg, 0.45 mmol) and a stirring bar. The flask was evacuated, filled with argon three times and 10 mL toluene were added. The yellow solution was stirred for 10 min. Then, hexadecane (590 μ L, 2 mmol), aryl bromide (10 mmol), and TMEDA (1.12 mL, 7.5 mmol) were added. Meanwhile, a 100-mL autoclave was charged with vinylboronic acid (15 mmol, 2.22 g), evacuated and filled with argon three times. Subsequently, the yellow solution was transferred to the autoclave *via* syringe. After the autoclave had been purged with CO several times, the reaction was run at 2.5 bar CO and at 80–100 °C. After 24 h the reaction was finished. The autoclave was cooled to ambient temperature and a sample was taken to determine the yield of the first step by GC. Without opening the autoclave, a solution of dioxane (15 mL) and 37% HCl (832 μ L, 10 mmol) was transferred by syringe into the autoclave. The second reaction was carried out at 40 bar CO and 100 °C for 20 h. After cooling to room temperature, the reaction solution was transferred to a 250-mL round-bottom flask containing 50 mL MeOH. From this solution, 200 μ L were reacted with trimethylsilyldiazomethane to give the corresponding ester. Subsequently, the reaction solution was filtered, 98% H₂SO₄ (110 μ L) was added and the solution was refluxed for 5 h. Finally, the solvent was evaporated and the formed ester was further purified by chromatography or crystallization.

Experimental Procedure for the 51-g Scale Synthesis of Ketoprofen

According to our synthetic protocol for 2-(diarylcarbonyl)-methyl propionate, we charged a 2-L autoclave with bromobenzene (21.02 mL, 200 mmol). We obtained 39.8 g (74%) of the methyl ester of Ketoprofen. To isolate the free acid,

we added 50 mL of 20% NaOH solution and 50 mL of MeOH. The mixture was refluxed for 1 h and MeOH was removed under vacuum. The solution was acidified to pH 2 by 2N HCl, extracted with diethyl ether three times and washed with brine. After drying with NaSO₄, the solvent was removed and 37.4 g (73.5%) of a viscous yellow product was obtained.

Methyl Ester of Ketoprofen: Yield: 60%; light yellow oil; *R*_f (EE/heptane=1:10): 0.17; ¹H NMR (300 MHz, CDCl₃): δ =7.82–7.80 (m, 2H, 2CH), 7.75 (dd, *J*=1.6 Hz, 1H, CH), 7.68 (dpt, *J*=7.5, 1.6 Hz, 1H, CH), 7.63–7.56 (m, 1H, CH), 7.54 (dpt, *J*=7.7, 1.6 Hz, 1H, CH), 7.51–7.40 (m, 3H, 3CH), 3.81 (q, *J*=7.3 Hz, 1H, CHCH₃), 3.68 (s, 3H, OCH₃), 1.54 (d, *J*=7.3 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ =196.9 and 175.0 (2CO), 141.3, 138.4 and 137.9 (3C), 132.9, 131.9, 130.0, 130.0, 129.2, 129.0, 128.5, 128.3, 128.3 (9CH), 52.1 and 45.2 (CHCH₃, OCH₃), 18.5 (CH₃); MS (70 eV): *m/z* (%)=268 (42) [M⁺], 209 (100), 191 (23), 105 (51), 77 (36); IR (ATR): ν_{max} =2950 (w), 1734 (s), 1657 (s), 1597 (w), 1580 (w), 1447 (m), 1434 (m), 1317 (m), 1281 (s), 1207 (s), 1165 (s), 1075 (m), 1024 (w), 999 (w), 978 (w), 950 (m), 859 (w), 820 (w), 788 cm⁻¹ (w); anal. calcd. for C₁₇H₁₆O₃: C 76.10, H 6.01; found: C 76.07, H 6.22.

Methyl Ester of Suprofen: Yield: 68%; light yellow solid, mp 53 °C; *R*_f (EE/heptane=1:5): 0.19; ¹H NMR (300 MHz, CDCl₃): δ =7.84 (d, *J*=8.5 Hz, 2H, CH), 7.42 (d, *J*=8.5 Hz, 2H, CH), 7.72 (dd, *J*=4.9, 1.2 Hz, 1H, CH), 7.65 (dd, *J*=3.8, 1.2 Hz, 1H, CH), 7.16 (dd, *J*=4.9, 3.8 Hz, 1H, CH), 3.82 (q, *J*=7.2 Hz, 1H, CHCH₃), 3.69 (s, 3H, OCH₃), 1.55 (d, *J*=7.2 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ =187.7 and 174.3 (2CO), 144.9, 143.6 and 137.0 (3C), 134.8, 134.2, 129.7, 129.7, 128.0, 127.7, 127.7 (7CH), 52.3 and 45.5 (CHCH₃, OCH₃), 18.5 (CH₃); MS (70 eV): *m/z* (%)=274 (56) [M⁺], 215 (100), 111 (53), 103 (10); IR (ATR): ν_{max} =3099 (w), 2947 (w), 1727 (s), 1630 (s), 1604 (m), 1514 (w), 1431 (w), 1414 (s), 1326 (w), 1284 (s), 1261 (s), 1232 (m), 1203 (s), 1161 (s), 1128 (w), 1085 (w), 1060 (m), 1012 (w), 964 (w), 886 (w), 866 (m), 845 (m), 807 (w), 774 (w), 737 (s), 695 cm⁻¹ (w); anal. calcd. for C₁₅H₁₄O₃S: C 65.67, H 5.14, S 11.69; found: C 65.89, H 5.11, S 11.73.

Methyl 2-[4-(4-methoxybenzoyl)phenyl]propionate: Yield: 45%; light yellow oil; *R*_f (EE/heptane=1:10): 0.15; ¹H NMR (300 MHz, CDCl₃): δ =7.82 (d, *J*=8.9 Hz, 2H, Ph), 7.72 (d, *J*=8.4 Hz, 2H, Ph), 7.40 (d, *J*=8.4 Hz, 2H, Ph), 6.96 (d, *J*=8.9 Hz, 2H, Ph), 3.88 (s, 1H, OCH₃), 3.81 (q, *J*=7.2 Hz, 1H, CHCH₃), 3.69 (s, 1H, OCH₃), 1.54 (d, *J*=7.2 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ =195.1 and 174.5 (2CO), 163.3, 144.6, 137.2 and 130.1 (4C), 132.6, 130.2, 127.4 and 113.6 (4CH), 55.5, 52.3 and 45.5 (2 OCH₃, CHCH₃), 18.5 (CH₃); MS (70 eV): *m/z* (%)=298 (95) [M⁺], 239 (81), 211 (32), 191 (17), 135 (100), 103 (10), 77 (16); IR (ATR): ν_{max} =2979 (w), 2951 (w), 1734 (s), 1649 (m), 1598 (s), 1508 (w), 1456 (w), 1416 (w), 1305 (m), 1281 (m), 1252 (s), 1208 (m), 1169 (s), 1147 (s), 1116 (w), 1068 (w), 1026 (m), 965 (w), 928 (s), 840 (m), 773 (m), 753 (m), 687 cm⁻¹ (m); anal. calcd. for C₁₈H₁₈O₄: C 72.47, H 6.08; found: C 72.66, H 6.01.

Methyl 2-[4-(4-trifluoromethylbenzoyl)phenyl]propionate: Yield: 70%; light yellow oil; *R*_f (EE/heptane=1:10): 0.10; ¹H NMR (300 MHz, CDCl₃): δ =7.89 (d, *J*=8.3 Hz, 2H, Ph), 7.80–7.72 (m, 4H, Ph), 7.44 (d, *J*=8.3 Hz, 2H, Ph), 3.83 (q, *J*=7.2 Hz, 1H, CHCH₃), 3.69 (s, 1H, OCH₃), 1.55 (d, *J*=

7.2 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 195.0 and 174.2 (2CO), 145.9, 140.7, 135.6 (3C), 133.7 (q, ²J(C,F) = 32 Hz, C), 130.5, 130.1 and 127.8 (3CH), 125.3 (q, ³J(C,F) = 3.9 Hz, CH), 120.1 (q, ¹J(C,F) = 174 Hz, CF₃), 52.2 and 45.4 (OCH₃, CHCH₃), 18.4 (CH₃); MS (70 eV): *m/z* (%) = 336 (34) [M⁺], 277 (100), 191 (15), 173 (45), 145 (28); IR (ATR): ν_{max} = 2984 (w), 2953 (w), 1736 (m), 1663 (m), 1606 (s), 1408 (w), 1323 (s), 1311 (s), 1277 (s), 1209 (m), 1164 (s), 1125 (s), 1109 (s), 1064 (s), 1017 (m), 930 (s), 860 (m), 773 (m), 757 (m), 690 cm⁻¹ (m); anal. calcd. for C₁₈H₁₅F₃O₃: C 64.28, H 4.50; found: C 64.49, H 4.65.

Acknowledgements

The authors thank S. Giertz, Dr. R. Jackstell and Dr. H. Klein (all at Leibniz Institute for Catalysis) for excellent technical assistance. Generous financial support from Mecklenburg-Vorpommern, the Fonds der Chemischen Industrie, the Bundesministerium für Bildung und Forschung (BMBF), and the DFG (Leibniz-Price) is gratefully acknowledged.

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