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Article

Transition-Metal Catalyzed Synthesis of Ketoprofen

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Reações catalisadas por complexos de metais de transição tais como carbonilação, hidrovinilação e hidrogenação foram empregadas na síntese do ácido α-(3-benzoilfenil)propanóico (Cetoprofeno). Acoplamento do tipo Heck entre 3-bromobenzofenona e etileno conduziu à 3-vinilbenzofenona que na sequência, por carbonilação catalisada por paládio, foi tranformada no α-(3-benzoilfenil)propanoato de isopropila com rendimento de 95% e regiosseletividade >99,5%. Hidrólise deste éster conduziu ao Cetoprofeno com 90% de rendimento. Cetoprofeno foi também obtido em duas etapas a partir da 3-vinilbenzofenona *via* reação de hidrovinilação catalisada por níquel que conduz seletivamente ao 3-(3'-benzoilfenil)-1-buteno (96%), seguido por oxidação desta olefina em ácido. A 3-etenilbenzofenona pôde ser sintetizada a partir da 3-bromobenzofenona *via* uma reação de acoplamento catalisada por paládio. Este alcino foi carabonilado em presença de paládio conduzindo regiosseletivamente (97%) ao α-(3-benzoilfenil)acrilato de metila. A hidrólise do éster conduz ao ácido α-(3-benzoilfenil)acrílico que foi então hidrogenado enantiosseletivamente ao (S)-Cetoprofeno (95% e.e.) usando um complexo Ru-(S)-BINAP como catalisador.

Transition metal-catalyzed reactions including carbonylations, hydrovinylations and hydrogenations have been applied in the synthesis of α-(3-benzoylphenyl)propanoic acid (Ketoprofen). 3-Vinylbenzophenone was obtained from 3-bromobenzophenone by a Pd-catalyzed Heck coupling reaction. Pd-catalyzed carbonylation of this olefin gave the isopropyl α-(3-benzoylphenyl) propionate in high yield (95%) and with high regioselectivity (>99.5%). Ketoprofen was obtained in 90% yield by hydrolysis of the isopropyl ester. It was also obtained in two steps from 3-vinylbenzophenone by a Ni-catalyzed hydrovinylation selectively affording 3-(3'-benzoylphenyl)-1-butene, followed by an oxidation. 3-Ethynylbenzophenone was obtained from 3-bromobenzophenone by Pd-catalyzed coupling reaction. By means of a Pd-catalyzed carbonylation, this alkyne was converted regioselectively (97%) into methyl α-(3-benzoylphenyl) acrylate (93% yield). Hydrolysis of the ester afforded the α-(3-benzoylphenyl)acrylic acid. Asymmetric hydrogenation of this acid to give (S)-ketoprofen in 95% optical yield was achieved using a chiral Ru-(S)-BINAP catalyst.

Keywords: ketoprofen, carbonylation, hydrovinylation, hydrogenation

Introduction

Homogeneous catalysis has been responsible for many major recent developments in synthetic organic chemistry[1,2]. The combined use of organometallic and coordination chemistry has led to a number of new powerful synthetic methods involving the selective formation and/or cleavage of C-C and C-heteroatom bonds. An appropriate choice of central metal and a careful molecular design of coordinated ligands, especially with regard to electronic and steric properties, have resulted in the development of active and selective (chemo-, regio- and enantioselective) catalytic systems. Over the past years we have focused our attention on the synthesis of transition metal complexes[3], and their application in the selective transformation of organic unsatured substrates[4-10].

α-Arylpropionic acids are an important class of non-steroidal anti-inflammatory agents with a multibillion-dollar market[11]. Among the numerous methodologies[12,13] for the synthesis of this class of drug, metal-catalyzed reactions appear to be of general utility and are very promising in racemic and asymmetric synthesis. In this work we show the application of homogeneous metal-based catalytic systems for the synthesis of Ketoprofen (Scheme 1).

Ketoprofen was developed by Rhône-Poulenc[14] and is commercialized in its racemic form in Brazil by Rhodia as Profenid. The synthesis of ketoprofen generally involves a multi-step reaction procedure[12]. Although many asymmetric syntheses for α-arylpropionic acids have been devel-

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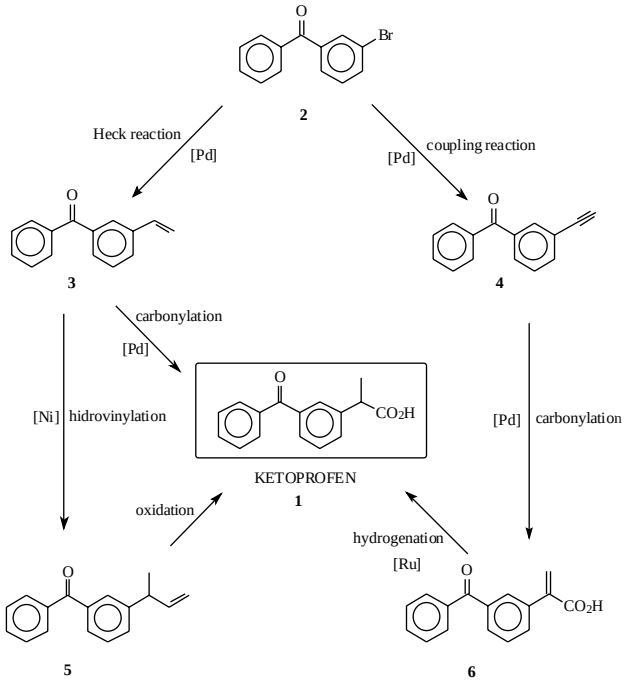
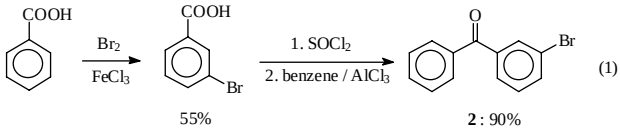


Scheme 1

oped, most of them are not amenable to Ketoprofen. In terms of enantioselective catalytic reactions, asymmetric hydrogenation[15] and epoxidation[16] reactions have been used as key steps. The hydrogenation of α-(3-benzoylphenyl) acrylic acid using a chiral rhodium catalyst gave Ketoprofen in moderate enantiomeric excess (up to 69%)[15]. Another catalytic approach made use of a combination of Sharpless epoxidation followed by a stereoselective hydrogenolysis of a benzylic carbon-oxygen bond to establish the stereochemistry[16]. Using this approach, (S)-Ketoprofen was obtained in 98% ee in 11 steps starting from 3-bromoacetophenone. The other asymmetric syntheses described are not catalytic reactions and the stereoselectivity is achieved using a stoichiometric chiral auxiliary. For instance, α-(3-benzoylphenyl)acetic acid was transformed into a chiral imide using oxazolidines as chiral auxiliaries[17]. Thereafter, the chiral imide was alkylated with methyliodide. Racemizing amide cleavage conditions did not afford (S)-Ketoprofen of sufficient enantiomeric purity and a later separation by recrystallisation of diastereoisomers resulting from reaction with (R)-methylbenzylamine was necessary in order to obtain (S)-Ketoprofen in 96% ee. Another approach started from racemic Ketoprofen which was transformed into a ketene[18,19]**.** Diastereoselectivities for the addition of a chiral hydroxyl compound were, after saponication, Ketoprofen up to 71% for the chiral lactate[18] and up to 99% for (R)-pantolactone[19]. Finally, a photochemical rearrangement of α-chloropropiophenones was used to obtain α-arylpropionic acids in low optical yield in the case of Ketoprofen (32%)[20].

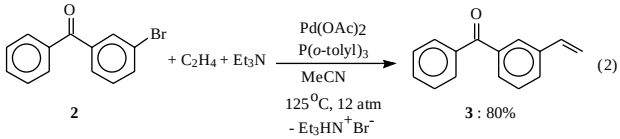
Results and Discussion

As depicted in Scheme 1, the starting material for different pathways in the synthesis of Ketroprofen (**1**) is 3-bromobenzophenone (**2**). This aryl bromide was prepared in two steps from benzoic acid (Eq. 1)[20]. First, bromination of benzoic acid gave 3-bromobenzoic acid in 55% yield. Second, the acid was converted into the acid chloride with $SOCl_2$ which by a Friedel-Crafts reaction with $AlCl_3$ and benzene afforded **2** in 90% yield.



*Heck reaction: synthesis of 3-vinylbenzophenone (**3**) and 3-ethynylbenzophenone (**4**)*

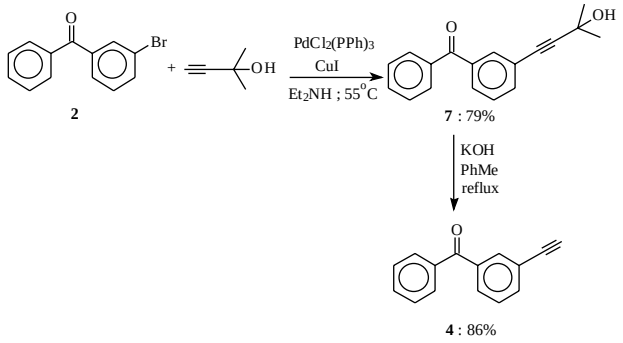
3-Vinylbenzophenone (Eq. 2) and 3-ethynylbenzophenone (Scheme 2) can be obtained from **2** by a palladium-catalyzed coupling[21]. Coupling of 3-bromobenzophenone with ethylene was carried out under Heck conditions[22]. Thus, using a catalytic system composed of $Pd(OAc)_2$ and tri-o-tolylphosphine, **2** dissolved in acetonitrile, was coupled with ethylene (20 atm) at 125°C giving 3-vinylbenzophenone (**3**) in good yield (80%).



3-Bromobenzophenone was coupled with 2-methyl-3-butyn-2-ol, an oily acetylene equivalent, under the Hagiahara's conditions[23] to give 1-(3'benzoylphenyl)-3-methyl-1-butyn-3-ol (**7**). Thus, using a catalytic system composed of $PdCl_2(PPh_3)_2$ and copper(I) iodide, **2** dissolved in diethylamine was coupled with **3** under reflux for 17 h to afford **7** in good yield (79%). This compound upon treatment with alkali[24] was converted into 3-ethynylbenzophenone (**4**) in 86% yield.

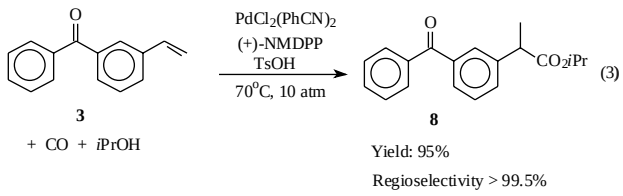
*Palladium-catalyzed carbonylation of 3-vinylbenzophe-none (**3**)*

The transition metal-catalyzed carbonylation of organic substrates represents a very important process in organic synthesis. Indeed, carbon monoxide can be



Scheme 2

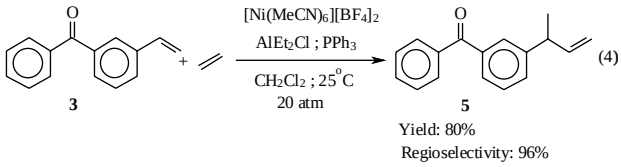
directly introduced into unsaturated substrates to produce organic molecules such as aldehydes, ketones, esters, amides, and other carbonyl-containing functionalities[25]. Although many transition metal complexes are effective catalysts for carbonylation, palladium complexes are the most widely employed. In this respect, palladium-catalyzed carbonylation of styrene derivatives in the presence of alcohols (hydroesterification) affords α-arylpropionic esters that are converted into α-arylpropionic acids by hydrolysis. Recently, we demonstrated that palladium-based catalysts associated with a phosphine ligand and immobilized in 1-n-butyl-3-methylimidazoliumtetrafluoroborate are highly efficient for the biphasic regioselective hydroesterification of styrene derivatives under mild conditions[4]. The choice of the phosphine ligand is crucial on the regioselectivity and activity control and the best results were found using (+)-neomenthyldiphenylphosphine [(+)-NMDPP]. These conditions were applied to the carbonylation of 3-vinylbenzophenone in homogeneous media (Eq. 3).



The carbonylation of **3** dissolved in a mixture isopropanol (4 mL)/cyclohexane (6 mL) proceeds under 10 atm of CO at 70°C for 20 h using a catalytic system composed of $PdCl_2(PhCN)_2$, (+)-NMDPP, and *p*-toluenesulfonic acid. Isopropyl α-(3 benzoylphenyl) propionate (**8**) was obtained in high yield (95%) and high regioselectivity (α : β > 99.5 : 0.5). Hydrolysis of the isopropyl ester with aqueous KOH followed by acidification with HCl gave Ketoprofen in 90% yield.

*Nickel-catalyzed hydrovinylation of 3-vinylbenzophenone (**3**)*

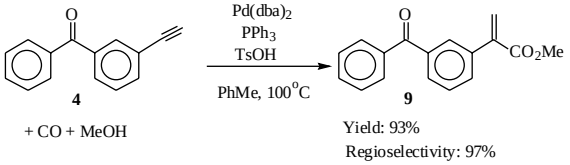
The catalytic hydrovinylation of styrene derivatives can be used to produce 3-aryl-1-butenes[26]. These olefins are converted into α-arylpropionic acids by an oxidation reaction[27]. Moreover, they have also been used as monomers for the homopolymerization or copolymerization of olefins. We have shown that a catalytic system composed of $[Ni(MeCN)_6][BF_4]_2$, triphenylphosphine and diethylaluminum chloride is active and regioselective for the hydrovinylation of styrene and alkylstyrenes[7]. However, low activities or inactivity were observed for styrene derivatives containing a Lewis basic group. Further studies have shown that these styrene derivatives can also be hydrovinylated by changing the relative ratios of the three catalyst components [28]. After intensive investigation of the hydrovinylation of 3-vinylbenzophenone we have pinpointed the reaction conditions and procedure which afford 3-(3'-benzoylphenyl)-1-butene (**5**) with both a high regioselectivity and yield (Eq. 4).



The hydrovinylation reaction was carried out using an Al/Ni ratio = 25 and PPh_3/Ni ratio = 4 to afford the hydrovinylated product in 80% isolated yield and 96% regioselectivity. It is interesting to note that in this case the addition order is crucial. In fact 3-vinylbenzophenone must be introduced only after the *in situ* formation of the catalyst (see experimental section). If it is introduced first, as described for the hydrovinylation of styrene[7], the carbonyl group in **3** can interact with the organoaluminum Lewis acid preventing the formation of the nickel-hydride catalytic species. The observed chemoselectivity is presumably the result of the Ni-H bond reacting faster with the activated C=C bond of **3** than with that of ethylene and/or the higher stability of the η^3-benzylic-nickel compared with an ethylnickel intermediate. Steric effects of the triphenylphosphine ligand prevent a second styrene molecule from approaching the resulting Ni-C bond, but not the smaller ethylene molecule, and as a result **3** is almost exclusively hydrovinylated as 3-(3'-benzoylphenyl)-1-butene (**5**) and neither oligomerized or polymerized. Ketoprofen was obtained in 65% yield by oxidation of **5** with $KMnO_4/NaIO_4$.

*Palladium-catalyzed carbonylation of 3-ethynylbenzo-phenone (**4**)*

Recently we described a simple method for the synthesis of chiral α-arylacrylic esters by the carbonylation of arylacetylenes in the presence of chiral alcohols catalyzed by palladium complexes under mild conditions with high yields[5]. Two regioisomers can be obtained (α and β-arylacrylic esters) and the regioselectivity depends on the phosphine ligand used. The selective carbonylation of **4** was performed using a catalytic system composed of $Pd(dba)_2$, PPh_3 and *p*-toluenesulfonic acid (Eq. 5). In the presence of methanol and operating under mild conditions (10 atm, 100°C, 2 h), this catalytic system affords the methyl α-(3-benzoylphenyl)acrylate (**9**) in a very good yield (93%) and with high regioselectivity (α : β = 97 : 3). Hydrolysis of the methyl ester **9** with aqueous KOH followed by acidification with HCl gave the α-(3-benzoylphenyl) acrylic acid (**6**) in almost quantitative yield.



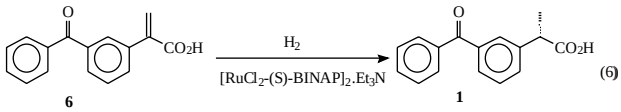
(5)

*Ruthenium catalyzed asymmetric hydrogenation of α-(3-benzoylphenyl)acrylic acid (**6**)*

The anti-inflammatory activity of α-arylpropionic acids resides in the (S)-isomers but, with the exception of Naproxen where the (R)-isomer is a liver toxin, they are currently administered as racemates. However, in recent years the use of enantiomerically pure drugs has become almost mandatory not only to achieve enhanced specificity of drug action but to avert the possible toxicity and undesirable load on metabolism by the other enantiomer[29].

(S)-Ketoprofen was obtained in moderate optical yield (up to 67%) by asymmetric hydrogenation of α-(3-benzoylphenyl)acrylic acid using a rhodium homogeneous catalyst and (-)-DIOP as a chiral phosphine ligand[15]. A significant advance in chiral synthesis involves asymmetric hydrogenation reactions of α,β-unsaturated acids catalyzed by Ru-BINAP complexes[30]. Noyori has demonstrated that the complex $[(S)\text{-BINAP}]Ru(OAc)_2$ catalyzes the hydrogenation of α-(6-methoxy-2-naphtyl)acrylic acid to (S)-Naproxen in 92% chemical yield and with an enantiomeric purity of 97%[31]. Despite the relatively high pressure required (135-150 atm) for the reaction that may present a practical limitation, Monsanto patented an industrial process for the synthesis of (S)-Naproxen where the key-step is this asymmetric hydrogenation reaction[11]. Recently, we have shown that the asymmetric hydrogenation of α-arylacrylic acids can be performed in presence of *in situ* or preformed Ru-BINAP catalyst precursors immobilized in an ionic liquid phase[6]. In comparison with the homogeneous reaction, similar or slightly increased optical yields were obtained. It is interesting to note that no significant effect of the hydrogen pressure was observed. At the end of the reaction the hydrogenated product can be separated by simple decantation and the ionic catalyst solution can be recycled without significant changes in activity and selectivity.

We performed the hydrogenation of α-(3-benzoylphenyl) acrylic acid (**6**) in homogeneous media using the commercially available $[RuCl_2\text{-(S)-BINAP}]_2.Et_3N$ as catalyst (Eq. 6). The reaction was carried out in methanol at room temperature giving Ketoprofen in good yield. Although Ru-BINAP complexes have also been used in the hydrogenation of ketones[30], only hydrogenation of the C=C bond was observed under the conditions employed. On the other hand, the optical yields of the hydrogenation products depended on the reaction conditions. Under the conditions studied the optical yield in (S)-Ketoprofen improved from 43 to 70% upon increasing the hydrogen pressure from 30 to 70 atm. In addition, an increase in the optical yield of (S)-Ketoprofen was observed due to the lowering of the temperature and the addition of an organic base. When the reaction was carried out at –5°C and using triethylamine (NEt_3/substrate = 1) as a base promoter, (S)-Ketoprofen was obtained in 95% ee. Compared with the literature[12-20], these results are a significant improvement in terms of the enantioselective synthesis of (S)-Ketoprofen. It is worthwhile to mention that the racemic catalytic carbonylation and hydrovinylation reactions described herein should be transposable into an asymmetric variant if a suitable chiral catalyst is found and this work is in progress.



(6)

(S)-KETOPROFEN

H_2 (atm)	T (°C)	NEt_3/substrate	% e.e.
25	25	0	43
85	25	0	70
85	- 5	1	95

Conclusions

In this work, metal-catalyzed processes such as the Heck reaction, carbonylation, hydrovinylation and asymmetric hydrogenation were applied for the synthesis of an α-arylpropionic acid (Ketoprofen) by different pathways. In each

reaction, through the suitable choice of transition metal complex, ligand and experimental conditions, we have found an active catalytic system that operates under mild conditions with high selectivity.

Experimental

General experimental procedures

Catalytic reactions were performed under argon by standard manipulation of air-sensitive compounds. NMR spectra were recorded on a Varian VXR-200 or Varian XL 300. Infrared spectra were recorded on a Bomem B-102 spectrometer. Mass spectra were recorded on a GC/MS Shimadzu QP-5050 (EI, 70eV). Optical rotation values were recorded on a Perkin Elmer 341 polarimeter at 20°C.

Solvents were dried under adequate drying agents and distilled under argon prior to use. $Pd(dba)_2$[32], $PdCl_2(PhCN)_2$[33], $PdCl(PPh_3)_2$[34], $[Ni(MeCN)_6][BF_4]_2$[3], 3-bromobenzophenone[20] were synthesized as described in the literature. $[RuCl_2$-(S)-BINAP$]_2.NEt_3$ and $Pd(OAc)_2$ were purchased from Strem and used without further purification. The other reagents were purchased from Aldrich and used without further purification.

3-Vinylbenzophenone (**3**)

A solution of **2** (2.61 g, 10 mmol), palladium acetate (22.2 mg, 0.1 mmol) and tri-*o*-tolylphosphine (62 mg, 0.20 mmol) in CH_3CN (10 mL) and NEt_3 (5 mL) was placed in a stainless steel autoclave under argon. Ethylene was introduced at the desired pressure (12 atm) with stirring to saturate the solution. The autoclave was stirred magnetically in an oil bath at 125°C for 4 h. After cooling at room temperature and releasing the excess ethylene, the autoclave was opened. Water was added to the reaction mixture and the product was extracted with ether. The organic layer was dried over $MgSO_4$, filtered off and the volatiles were removed under reduced pressure affording an orange oil. The crude product was purified by flash chromatography on silica gel (hexanes:ethyl acetate = 9 : 1) giving **3** as a colorless oil (1.66 g, 80 %). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.32 (d, *J* 10.85 Hz, 1H), 5.80 (d, *J* 17.60 Hz, 1H), 6.76 (dd, *J* 10.85 Hz, *J* 17.67 Hz, 1H), 7.24 – 7.82 (m, 9H). IR (ν_{max}/cm^{-1}) 3082, 3058, 1660, 1625, 1597, 1447, 1316, 1280, 703 (neat). GC-MS (70 eV): 208 (M^+,74%), 131(99%), 105(100%), 103 (35%), 77(92%), 51(41%).

3-Ethynylbenzophenone (**4**)

2 (620 mg, 2.38 mmol), $PdCl_2(PPh_3)_2$ (16.7 mg, 0.024 mmol), and copper(I) iodide (4.6 mg, 0.024 mmol) were placed in a Schlenk tube under argon. To this mixture were added diethylamine (10 mL) and 2-methyl-3-butyn-2-ol (300.3 mg, 3.57 mmol), and the resulting mixture was heated to reflux for 23 h. The insoluble material was filtered off and the excess diethylamine was evaporated under reduced pressure. The residue was dissolved in ether (30 mL) and washed successively with saturated aqueous NaCl, 10% aqueous citric acid (3 x 20 mL), saturated aqueous NaCl (20 mL) , 5% aqueous $NaHCO_3$ (20 mL), and finally with saturated aqueous NaCl (20 mL), then dried over anhydrous $MgSO_4$. Kugelrohr distillation at 2 mm Hg and at 145°C gave **7** as colorless oil (353 mg, 79 %)[GC-MS (EI, 70 eV): 264 (M^+, 15%), 249 (66%), 171 (35%), 159 (19%), 115 (15%), 105 (100%), 77 (64%), 51 (27%)].A mixture of **7** (353 mg, 1.34 mmol), powdered potassium hydroxide (33.5 mg, 0.6 mmol) and toluene (10 ml) was heated to reflux for 4 h under an argon atmosphere. The excess toluene was evaporated under reduced pressure, and the residue was dissolved in ether (30 mL). The ethereal solution was washed successively with saturated aqueous NaCl (20 mL), 10% aqueous citric acid (3 x 20 mL), saturated aqueous NaCl (20 mL), 5% aqueous $NaHCO_3$ (20 mL) and finally with saturated aqueous NaCl (20 mL). The solution was dried over anhydrous $MgSO_4$, filtered and evaporated. Kugelrohr distillation at 2 mm Hg and 125°C gave **4** as colorless oil (218 mg, 80 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.12 (s, 1H), 7.44-7.84 (m, 9H). IR (ν_{max}/cm^{-1}) 3290, 2923, 2111, 1662, 1597, 1448, 1318, 1283, 720 (neat). GC-MS (EI, 70 eV): 206 (M^+, 51%), 129 (44%), 105 (100%), 101 (35%), 77 (57%), 75 (19%), 51 (44%), 50 (14%).

Carbonylation of 3-vinylbenzophenone (**3**)

In a 100 ml-stainless steel autoclave under argon were placed $PdCl_2(PhCN)_2$ (2.1 mg, 0.0055 mmol), (+)-NMDPP (3.8 mg, 0.012 mmol), *p*-toluenesulfonic acid (4.6 mg, 0.027 mmol), **3** (100 mg, 0.48 mmol), isopropanol (4 mL) and cyclohexane (6 mL). The reactor was pressurized with 10 atm of CO and the reaction mixture was stirred at 70°C for 20 h. After cooling and releasing the excess carbon monoxide, the reaction mixture was analyzed by GC using naphthalene as an internal standard. Methyl α-(3-benzoylphenyl) propionate (**8**) [GC-MS (EI, 70 eV): 296 (M^+, 2%), 210 (40%), 209 (53%), 105 (100%), 103 (12%), 78 (11%), 77 (71%), 51 (18%)] was obtained in 95% GC yield and >99.5% regioselectivity. After concentration, water (10 mL) and KOH (150 mg) were added to the ester **8** and the mixture was stirred at room temperature for 24 h. The aqueous solution was washed with ether (3 x 10 mL) and acidified with concentrated HCl to pH 1. Ketoprofen was extracted with ether (3 x 30 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), water (2 x 10 mL) and dried with anhydrous $MgSO_4$.

Evaporation under vacuum gave Ketoprofen[15] (104 mg, 90%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (d, *J* 7.1 Hz, 3H), 3,78 (q, *J* 7.1 Hz, 1H), 7.35 – 8.39 (m, 9H), 9.4 (b, 1H). IR (ν_{max}/cm^{-1}) 3449, 3062, 2974, 1717, 1659, 1597, 1448, 1318, 1283, 720, 703 (neat).

Hydrovinylation of 3-vinylbenzophenone (**3**)

A solution of $[Ni(MeCN)_6][BF_4]_2$ (6.8 mg, 0.0132 mmol) and PPh_3 (14.8 mg, 0.0564 mmol) in dry CH_2Cl_2 (15 mL) was placed in a 100 mL stainless steel autoclave under argon. The autoclave was purged with ethylene and $AlEt_2Cl$ (0.2 mL, 1.8 mol L^{-1} solution in toluene) and styrene (100 mg, 0.96 mmol) were added to the system. The autoclave was closed and the mixture was stirred at room temperature for 10 min under an ethylene atmosphere. After this time, a solution of **3** (269 mg, 1.29 mmol) in dry CH_2Cl_2 (5 mL) was added and the resulting mixture was stirred at room temperature for 1 h under 10 atm of ethylene. After releasing the excess of ethylene, the autoclave was opened and the solvent was evaporated. Kugelrohr distillation at 2 mm Hg and 135^{o}C gave **5** as colorless oil (239 mg, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, *J* 7.08 Hz, 3H), 3.48 (q, *J* 6.81 Hz, 1H), 4.96 – 5.04 (m, 2H); 5.86 – 6.03 (m, 1H), 6.99 – 7.83 (m, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 43.0, 113.8, 128.1, 128.2, 128.4, 128.7, 130.0, 131.4, 132.3, 137.7, 142.6, 145.9, 196.8. GC-MS (EI, 70 eV) 236 (M$^+$, 22%), 159 (27%), 131 (80%), 105 (100%), 91 (15%), 77 (66%), 51(22%). IR (ν_{max}/cm^{-1}) 3082, 3076, 2965, 1659, 1598, 1577, 1447, 1440, 1282, 915, 715, 701 (neat).

Oxidation of 3-(3'-benzoylphenyl)-1-butene (**5**)

To a solution of **5** (90 mg, 0.38 mmol) in 10 mL of BuOH and 20 mL of water, $KMnO_4$ (185 mg, 1.17 mmol), $NaIO_4$ (1.46 g, 6.86 mmol) and K_2CO_3 (366 mg, 2.64 mmol) were added. The pH of the solution was adjusted to 8 with 3 mol L^{-1} aq NaOH and then the reaction mixture was stirred at room temperature for 3 h. After this time the pH of the mixture was adjusted to 1 with concentrated HCl and $NaHSO_3$ was added to reduce the MnO_2. The mixture was washed with ether and the ethereal layer was extracted with 3 mol L^{-1} aqueous NaOH. The aqueous layer was acidified with concentrated HCl and then extracted with ether. The organic layer was dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure, yielding α-(3-benzoylphenyl)propionic acid (Ketoprofen) as a colorless oil (63.2 mg, 65%).

Carbonylation of 3-ethynylbenzophenone (**4**)

In a 100 mL-stainless steel autoclave were placed **4** (218 mg, 0.9 mmol), bis-(dibenzylideneacetone)palladium (18.6 mg, 0,036mmol), PPh_3 (37.8 mg, 0.14 mmol), *p*-toluenesulfonic acid (6.2 mg, 0.036 mmol), MeOH (22 μL, 0.9 mmol) and toluene (15 mL). The mixture was stirred at 100^{o}C for 2 h under 10 atm of carbon monoxide. After cooling and releasing the excess carbon monoxide, the reaction mixture was filtered over Celite and the solvent was evaporated under reduced pressure. Methyl α-(3-benzoylphenyl)acrylate (**9**) was obtained in 93% GC yield and 97% regioselectivity [GC-MS (EI, 70 eV) 266 (M$^+$, 28%), 206 (15%), 189 (57%), 105 (100%), 102 (13%), 101 (13%), 77 (79%). After concentration, a 2 mol L^{-1} KOH aqueous solution (0.6 mL) and acetone (5 mL) were added to the ester **9** and the mixture was stirred at room temperature for 16 h. The aqueous solution was washed with ether (20 mL) and acidified with concentrated HCl to pH 1. The organic acid was extracted with ether (3 x 30 mL), washed with saturated aqueous NaCl (3x 30 mL) and dried with anhydrous Na_2SO_4. Evaporation under vacuum gave α-(3-benzoylphenyl) acrylic acid[35] (159 mg, 82%). ^{1}H NMR (200 MHz, $CDCl_3$,): δ6.10 (s, 1H), 6.61 (s, 1H), 7.29-8.00 (m, 9H), 9.40 (br, 1H).

Hydrogenation of α-(3-benzoylphenyl)acrylic acid (**6**)

In a 100 mL-stainless steel autoclave under argon were placed **6** (59 mg, 0.23 mmol), $[RuCl_2$-(S)-BINAP$]_2$.Et_3N (5.4 mg, 0.0032 mmol) and methanol (15 mL). The reactor was pressurized with hydrogen (25 atm) and stirred at room temperature for 22 h. After releasing the excess hydrogen, the reaction mixture was filtered over Celite and the solvent was evaporated under reduced pressure. The residue was then acidified with 10% HCl and extracted with ether (3 x 20mL). The ethereal extract was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure giving 53 mg of a mixture of **1** (91%) and **6** (9%). The optical rotation observed {$[\alpha]_D$ = +14^o (c=1.68 in CH_2Cl_2)} showed an excess of the (S)-Ketoprofen enantiomer. The mixture of hydrogenated and unhydrogenated acids was transformed into their methyl esters {methyl α-(3-benzoylphenyl)propionate: GC-MS (EI, 70 eV) 268 (M$^+$, 27%), 210 (12%), 209 (72%), 191 (19%), 105 (100%), 103 (20%), 78 (14%), 77 (95%)}. An enantiomeric excess of 43% was determined on a Varian-CX-3400 GC equipped with a chiral column CP-Chirasil-Dex CB (25m x 0,25 mm x 0,25 mmm); P_{H2} = 20 psi ; oven temperature = 150 (isotherm); methyl ester of (S)-ketoprofen = 49.4 min and methyl ester of (R)-ketoprofen = 50.8 min.

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