Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9641–9648

TETRAHEDRON

Access to racemic and enantioenriched 3-methyl-4-chromanones: catalysed asymmetric protonation of corresponding enolic species as the key step

Olivier Roy, François Loiseau, Abdelkhalek Riahi, Françoise Hénin* and Jacques Muzart

Unité Mixte de Recherche 'Réactions Sélectives et Applications', CNRS-Université de Reims Champagne-Ardenne, BP 1039, 51687 Reims Cedex 2, France

Received 13 March 2003; revised 2 September 2003; accepted 29 September 2003

Abstract—Brønsted acids induced the intramolecular cyclisation of 3-aryloxypropanoic esters affording 3-methyl-4-chromanones, which have been transformed into the corresponding racemic benzyl β-oxoesters. These latter esters, in the presence of hydrogen and catalytic amounts of both palladium and (*endo*, *endo*) aminoborneol, led to optically active chromanones with up to 75% ee through a deprotection–decarboxylation–protonation cascade reaction.

The synthesis of chromanones or their derivatives is of high interest in organic chemistry. In particular, 3-substituted-4-chromanones constitute the basic structure of natural products[1] possessing biological activities such as anti-mutagenic[2] and anti-inflammatory[3] properties. Therefore, our aim was to prepare optically active chromanones using a palladium induced cascade reaction analogous to that previously described for optically active cyclic[4] or linear[5] ketones (Fig. 1). For that purpose, the preparation of these chromanones in their racemic form was required. Many strategies have been proposed to prepare racemic 4-chromanones using disconnections a[6], b[7] or most frequently c,[8,9] both b and c being possibly carried out together[9,10] (Fig. 1). On the contrary, a few methods are available for the preparation of the same non racemic compounds starting from enantiopure synthons,[11] by using an external chiral ligand[12] or incorporating an enzymatic step.[13] A few examples of enantioenriched or enantiopure 3-hydroxychromanones have also been described.[14] The recent improvement of the enantioselective catalytic intramolecular Stetter reaction[15a] (disconnection d) to obtain highly enantioenriched chromanones[15b] incited us to present our own investigations for their preparation.

1. Preparation of starting racemic 3-methyl-4-chromanones and corresponding oxo esters

As we have recently disclosed the efficient synthesis of unsaturated esters **3** from Baylis–Hillman adducts **4**,[16] we envisaged to use these compounds to prepare **1** (Scheme 1).

Compound **3a** was first subjected to acidic Friedel–Crafts conditions using trifluoromethane sulfonic acid,[8a] (TfOH, 2 equiv.) in CH_2Cl_2 at room temperature. We only observed a Claisen transposition without any trace of the expected methylene chromanone; such a rearrangement has already been described, under more drastic thermal conditions[17] (Eq. (1)).

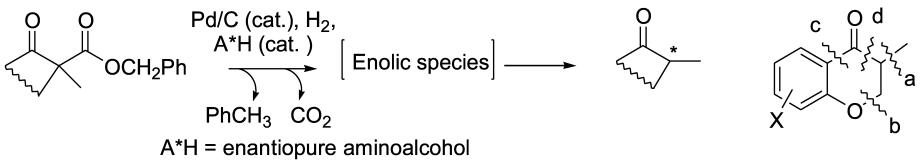
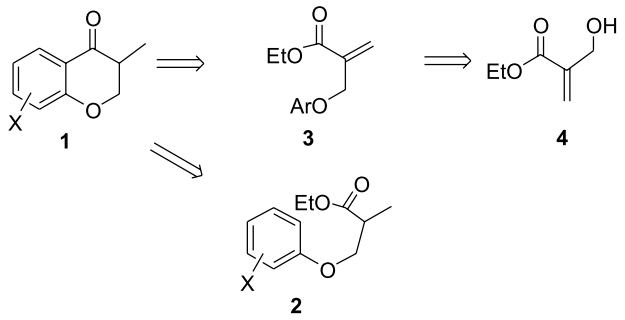


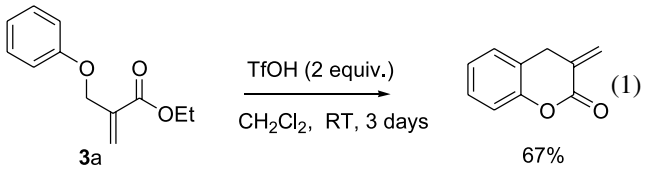
Figure 1. Target and envisaged methodology.

Keywords: 4-chromanones; Friedel–Crafts cyclisation; Brønsted acids; asymmetric catalysis; benzylic cleavage; decarboxylation; protonation; aminoborneol.
* Corresponding author. Tel.: +33-3-26-91-33-10; fax: +33-3-26-91-31-66; e-mail: francoise.henin@univ-reims.fr

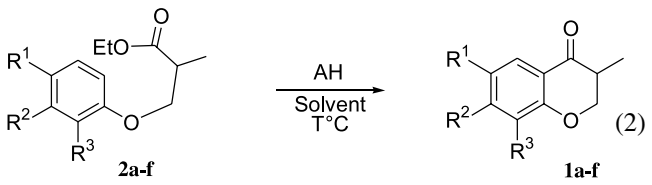
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.095



Scheme 1.



Hence, the methylenic double bond of **3** was hydrogenated over palladium leading to **2**, and we envisaged to submit the corresponding acids or acid chlorides to Friedel–Crafts cyclisation using reported methods.[8,9,11a,13,14c] However, the saponification experiments carried out with **2a** as the substrate were complicated by a competitive retro-Michael reaction, generating ethyl methacrylate beside phenol. Consequently, we investigate the electrophilic cyclisation directly from the ester. Actually, such a reaction has never been reported.



1, 2 a: R^1, R^2, R^3 = H; **b**: R^1 = OMe, R^2, R^3 = H; **c**: R^1 = Cl, R^2, R^3 = H; **d**: R^1 = *t*-Bu, R^2, R^3 = H; **e**: R^1, R^3 = H, R^2 = OMe; **f**: R^1, R^2 = H, R^3 = OMe

Preliminary cyclisation experiments using **2a** as substrate in the presence of Lewis acids ($AlCl_3$ and $TiCl_4$) were unsuccessful. Therefore, we examined Brønsted acids as promoters. The use of *p*-toluene sulfonic acid in toluene at reflux or under microwave activation[18] led to low yields (<30%), the degradation of starting material being mainly observed. With polyphosphoric acid, the results were also not satisfying, since only 39% of **1a** and degraded materials were obtained. The reaction became more effective when performed in methanesulfonic acid (MsOH) as solvent at 70°C (Table 1, entry 1). The decrease of the amount of MsOH and the use of dichloromethane or toluene as solvent had a large detrimental effect on the yields. Switching from MsOH to TfOH in refluxing toluene, allowed to reduce the acid quantity (entries 2–6); the molar ratio 3:1 of TfOH versus **2a** seemed to be optimum in terms of yield and conversion. The replacement of toluene by dichloromethane or benzotrifluoride led respectively to no or low conversion of **2a**. The reactivity of **2b**–**2f** was then examined leading to the expected compounds except from **2d** when TfOH was the promoter (entry 13). In this case, an elimination of the *t*-butyl group leading to **1a** through a reversal Friedel–Crafts alkylation was observed.[19] The retro-reaction did not occur with MsOH and the amount of this acid had to be decreased to 5 equiv. to obtain a fair yield of the expected product (entries 10–12). Starting from **2e**, the cyclisation occurred with a complete *para*-regioselectivity (entries 14, 15). Finally, starting from **2f** the yields of **1f** remained low, whatever the acid used as promoter (entries 16, 17).

Table 1. Cyclisation of **2** in the presence of Brønsted acids

Entry	Substrate	Acid (equiv.)	*T* (°C)	Time (h)	Conv. (%)	Product	Yield (%)[a]
1	**2a**	MsOH[b]	70	3.5	100	**1a**	69
2	**2a**	TfOH (0.25)[c]	Reflux	96	66	**1a**	37
3	**2a**	TfOH (0.6)[c]	Reflux	24	97	**1a**	72
4	**2a**	TfOH (2)[c]	Reflux	5.5	100	**1a**	77
5	**2a**	TfOH (3)[c]	Reflux	4.5	100	**1a**	95
6	**2a**	TfOH (4)[c]	Reflux	3	100	**1a**	86
7	**2b**	MsOH[b]	70	4.5	100	**1b**	50
8	**2c**	MsOH[b]	70	4	100	**1c**	86
9	**2c**	TfOH (3)[c]	100	15	100	**1c**	71
10	**2d**	MsOH[b]	80	2	100	**1d**	37
11	**2d**	MsOH (15)[c]	Reflux	24	100	**1d**	41
12	**2d**	MsOH (5)[c]	Reflux	72	92	**1d**	71
13	**2d**	TfOH (3)[c]	Reflux	1.3	100	**1a**	89
14	**2e**	MsOH[b]	80	2	100	**1e**	46
15	**2e**	TfOH (3)[c]	Reflux	6	97	**1e**	82
16	**2f**	MsOH[b]	80	5	100	**1f**	34
17	**2f**	TfOH (3)[c]	Reflux	15	71	**1f**	28

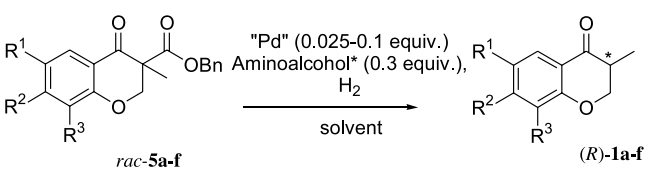
[a] Used as solvent (0.5 mL/mmol of **2**).
[b] In toluene as solvent (5 mL/mmol of **2**).
[c] Yields of purified compounds, the difference between conversions and yields corresponding to tarry material.

Thus, the synthetic scheme developed here is a convenient route to chromanones, starting from unexpensive, stable, safe and easily available materials.

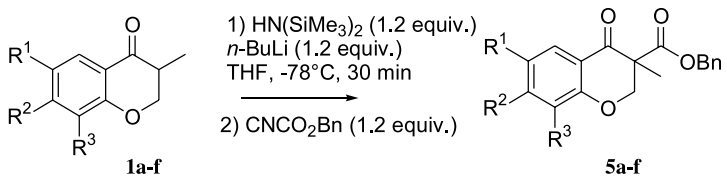
Chromanones **1a**–**1f** have been transformed to corresponding benzyl β-oxoesters **5a**–**5f** by selective C-carboxybenzylation of their enolates with benzyl cyanoformate[20] (Scheme 2, Table 2).

2. Enantioselective deprotection/decarboxylation/tautomerization

Compounds **5a**–**5f** were subjected to the cascade reaction already described elsewhere[4,5] by using catalytic amounts of both palladium on charcoal and a chiral protic source (Fig. 2), solvent and bubbling or gas bag of dihydrogen (Eq. (3)). This allowed the reductive cleavage of the benzyl group, then decarboxylation followed by asymmetric protonation of the resulting enolic species to afford **1** in its optically active form. Our investigations started with chloro-derivative **5c** leading to **1c** of known configuration.[11a,13]



rac-**5a-f** (*R*)-**1a-f** (3)



Scheme 2. Carboxybenzylation of **1**.

Table 2. Carboxybenzylation of **1**

1→5	R^1	R^2	R^3	Yield %
A	H	H	H	60
B	Ome	H	H	54
C	Cl	H	H	74
D	*t*-Bu	H	H	85
E	H	OMe	H	88
F	H	H	OMe	92

same order in ethyl acetate or acetonitrile (entries 6 and 10) and decreased in THF (entry 5), whereas the benzylic cleavage did not occur in toluene. No selectivity was observed in ethanol or DMF (entries 8 and 9). Working at room temperature seems to give the best result, since at 10°C, **5c** did not react and at 40 or 50°C **1c** was obtained with a lower ee (entries 2, 3 or 7). Such temperature effects have been noticed with linear compounds but differ from the results with substituted indanones or tetralones, where the higher ee's were reached at around 55°C.[4] As in cyclic

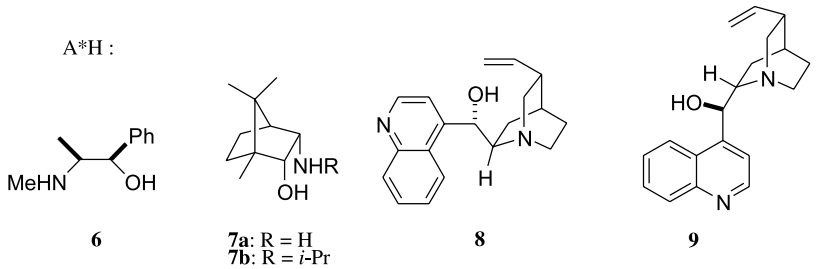


Figure 2. Aminoalcohols used as chiral protic sources.

A rapid screening of different parameters has been carried out (Table 3). If we compare the results with those observed starting from other cyclic[4] or linear[5] substrates, quite similar solvent effects will be noticed: the ee's of **1c** were of the same order as in cyclic series, aminoborneol **7a** was a better chiral protic source (entries 6 or 10) than (−) ephedrine, cinchonine and cinchonidine (entries 1, 13 and 14). Substituting the amino group of aminoborneol as in **7b** has no beneficial effect on the ee (entry 12). An amount of 0.3 equiv. of **7a** versus the substrate seemed appropriate since ee decreased by diminishing the amount of the chiral protic source (entries 10, 11).

Table 3. Cascade reaction from **5c**:[a] influence of the solvent, temperature and chiral protic source

Entry	A*H	Solvent	T (°C)	Time (h)	**1c** Yield (%)[b]	**1c** ee (%)[c] (config.)[d]
1	**6**	MeCN	22	3	98	32 (*R*)
2	**6**	MeCN	40	1.1	98	26 (*R*)
3	**6**	MeCN	50	1.15	97	24 (*R*)
4[e]	**6**	MeCN	22	1	98	28 (*R*)
5	**6**	THF	22	1	93	26 (*R*)
6	**7a**	MeCN	22	1	97	65 (*R*)
7	**7a**	MeCN	50	1	88	60 (*R*)
8	**7a**	EtOH	22	3	89	0
9	**7a**	DMF	22	nd[f]	89	0
10	**7a**	AcOEt	22	1	96	63 (*R*)
11	**7a**[g]	AcOEt	22	1	99	52 (*R*)
12	**7b**	MeCN	22	1	98	58 (*R*)
13	**8**	MeCN	22	6	98	22 (*S*)
14	**9**	MeCN	22	6	98	8 (*R*)

[a] 5% Pd/C Engelhard 5011 (0.0125 equiv.), A*H, 0.3 equiv., substrate, solvent, H_2 (gas bag or bubbling), the reaction time corresponds to the period required to reach full conversion of the substrate, as indicated by TLC.
[b] Isolated yields of purified products.
[c] Enantiomeric excess determined by HPLC.
[d] The configuration was attributed by comparison of the optical rotation with literature values.[13]
[e] Amount of Pd/C increased to 0.025 equiv.
[f] Not determined.
[g] A*H: 0.1 equiv. instead of 0.3 equiv.

Following these results, we extended the procedure to **5b** using **7a** as the chiral protic source but we did not notice any reproducible ee under the above cited conditions. A careful examination of experimental parameters led us to conclude that a strong influence of the supporting catalyst was responsible of this fact, as exemplified in Table 4. The ee's of **1b** varied from 13 to 69% by simple modification of the catalyst origin (entries 1–6). Palladium black finally gave us fair and reproducible results (entry 7). We have already observed that the selectivities from cyclic substrates were greatly influenced by the nature of the support[21] and this differs from the linear compounds.[5b] Such support effect has been reviewed[22] and largely discussed for in the heterogeneous enantioselective hydrogenation of α-oxoesters[23] or activated double bonds.[24] During selective reactions, an optimal geometry as an adequate surface coverage are required for adsorption of the chiral catalyst. The texture of the support, the surface area and the dispersion correspond to crucial parameters to obtain an active metal. In our case, the low surface area of palladium black was advantageous for the enantioselectivity (entry 7) as observed in isophorone reduction.[25] This was however not a general fact, since closer ee were reached in presence of palladium on charcoal from

Table 4. Cascade reaction from **5b**[a] in presence of **7**: influence of the heterogeneous support

Entry	Catalyst (equiv.)	Time[b] (h)	(*R*) **1b**	
			Yield (%)[c]	ee (%)[d]
1	5% Pd/C Engelhard 5011 (0.025)	1	99	13–50
2	5% Pd/C Engelhard 5067 (0.025)	1	99	28
3	5% Pd/C Janssen 1950205 (0.025)	1	99	33
4	10% Pd/C Janssen 1950306 (0.025)	1	78	48
5	10% Pd/C Johnson Matthey 490 (0.025)	4.5	88	67
6	10% Pd/C Acros 19503100 (0.025)	1.3	78	33
7	Pd black Janssen (0.1)	8.5	94	69

[a] Pd catalyst, **7a** (0.3 equiv.), **5b**, ethyl acetate, H_2 (gas bag or bubbling at room temperature).
[b] Time required to reach full conversion of the substrate, as indicated by TLC.
[c] Isolated yields of purified products.
[d] Enantiomeric excess determined by HPLC.

Johnson Matthey (entry 5). Furthermore, we did not observe such erratic results while using **5c**,[26] which suggests that the surface effect strongly depends on the substrate.

Afterwards, we used black palladium and **7a** to pursue our investigation and especially to evaluate the electronic effect due to the substituent pattern on the aryl group (Table 5). The ee of **1** varied from 60 to 75%, with the same value for **1b** and **1f** which both bear a methoxy group in *meta*-position of the chromanone carbonyle. The enantioselectivity correlates well with Hammett σ-values[27] and a linear Hammett plot was obtained except for **1e**[28–30] (Fig. 3). The slope of the line was determined to be -0.97 (R^2=0.99) and was slightly lower than that observed during the asymmetric protonation of enolates derived from Schiff bases.[31] As discussed when starting from open chain substrates,[5] one partial step responsible for the production of selectivity was favoured in the presence of electron donating groups. It is reasonable to assume that the faster reaction is also the more selective one, as pointed out for several selectivity examples.[32] This assertion agrees with the shorter reaction time (entry 4), corresponding to the more donor *t*-Bu group. According to the Hammett equation, our results suggest that the protonation of the enolic species corresponds to a key step, since it corresponds to the development of a positive

Table 5. Cascade reaction from **5a**–**5f** in the presence of **7a**[a]

Entry	Substrate	Time[b] (h)	Product	Yield (%)[c]	ee (%)[d] (configuration[e])
1	**5a**	8	**1a**	99	73 (*R*)
2	**5b**	8.5	**1b**	94	69 (*R*)
3	**5c**	9	**1c**	97	60 (*R*)
4	**5d**	4	**1d**	89	75 (*R*)
5	**5e**	7	**1e**	63	64 (*R*)
6	**5f**	8	**1f**	78	69 (*R*)

[a] Pd black, (0.1 equiv.), **7a** (0.3 equiv.), ethyl acetate, H_2 (gas bag or bubbling), room temperature.
[b] Time required to reach full conversion of the substrate, as indicated by TLC.
[c] Isolated yields of purified products.
[d] Enantiomeric excess determined by HPLC.
[e] Configurations determined by comparison of Cotton effects of compounds **1a**,**b**, **1d**–**f** with **1c** (see Experimental).

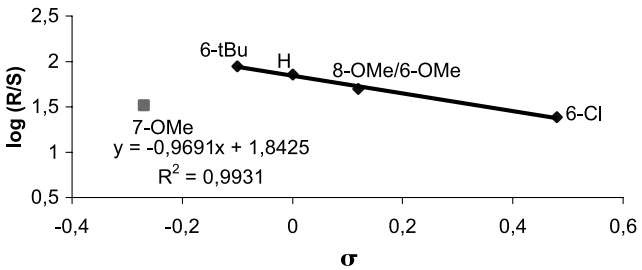


Figure 3. Plot at 22°C of log [selectivity] values for **5a**–**f** versus the corresponding Hammett constant σ.

charge in the transition state, namely the approach of a proton to the enolic species.

As shown in Figure 4, the structure of the enolic species has not been really ascertained. Since A*H is an aminoalcohol (Fig. 1), the amino group is basic enough to generate ammonium enolate **E**–**A**, starting from enol **E**–**H** or the ketoacid itself produced after deprotection of **5**. The existence of a palladium enolate species **E**–**Pd** could not be excluded, as the benzylic cleavage probably involves palladium insertion into the *O*-alkyl bond of the ester group. We have also observed the great influence of the nature of the catalyst on the reaction course. The quite elevated slope value corresponding to the Hammett line (nearly 1) is consistent with the participation of charged intermediates and transition states in the determining step. This is in favour of **E**–**A** or **E**–**Pd** and also allows to explain the deviation of the Hammett line starting from **5e**. The donating mesomeric effect of the methoxy group could destabilize an enolate as **E**–**A** or **E**–**Pd** before its protonation and thus induce a change in the rate determining step.

3. Conclusion

The present paper describes a convenient synthetic route to various substituted 3-methyl-4-chromanones from cheap and easily available starting material. It has also been established that the sequence deprotection, decarboxylation, asymmetric tautomerization can be successfully applied to the corresponding benzyl β-oxoesters to deliver the

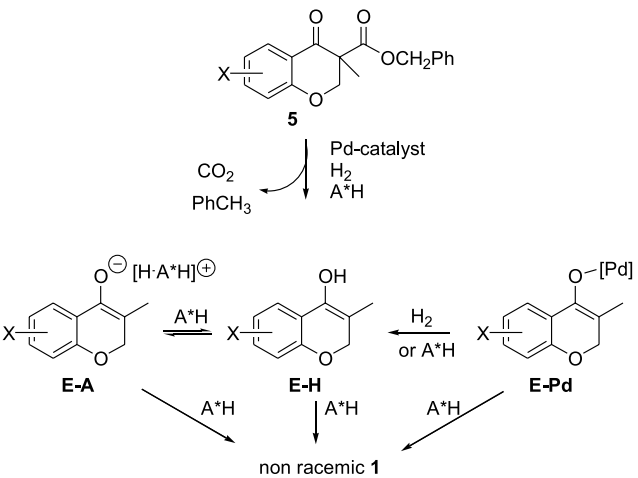


Figure 4. Possible structures of enolic species[5]

enantioenriched compounds in high yields. Using catalytic aminoborneol as the chiral protic source and palladium black as promoter, enantiomeric excess up to 75% could be achieved.

4. Experimental

4.1. General remarks

NMR Spectra: Bruker AC 250 (^{1}H, 250 or ^{13}C, 62 MHz) or Bruker AC 500 (^{1}H, 500 MHz or ^{13}C 124 MHz); internal TMS, $CDCl_3$ as solvent. Infrared spectra: FTIR Spectrafile IR plus midac. EI mass spectra: JEOL D-300 (70 eV) recorded at the Faculty of Pharmacy of Reims. Optical rotations: Perkin–Elmer 241 (0.5-dm cell). Circular dichroism: Jasco 810. Microanalysis: Perkin–Elmer CHN 2400. HPLC: Shimadzu LC10AS, UV SPD 10A detector (254 nm). Circular dichroism: JASCO 810. Chromatography: CCM, Alufolien Merck 5554 silica gel PF_{254}; flash chromatography, silica gel Merck 9385, 0.04–0.063 mm.

Purification of the solvents: ether and THF distilled from Na/benzophenone, dichloromethane, chloroform, ethyl acetate and toluene distilled over CaH_2, DMF over $MgSO_4$, acetonitrile over P_2O_5 and then CaH_2.

Compounds **3** have been previously described;[16] their hydrogenation to compounds **2** have been carried out under magnetic stirring in 2×10^{-4} M acetonitrile solutions, using 10% palladium on charcoal (Johnson Matthey 490) as catalyst (0.02 equiv./**3**) and gaseous hydrogen from a rubber balloon or a gas bag. After complete reaction (7–24 h, as indicated by TLC), the mixture is filtered over a pad of silica and solvent eliminated; the purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) led to compounds **2**.

4.1.1. Ethyl 2-methyl-3-phenoxypropanoate (2a). Colourless oil (2.32 g, 92%). IR (KBr): 2980; 1737; 1601; 1587; 1497 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.3 (m, 6H), 2.95 (sex, J=6.1 Hz, 1H), 4.02 (dd, J=9.2, 6.1 Hz, 1H), 4.15 (m, 3H), 6.85–6.97 (m, 3H), 7.24–7.32 (m, 2H). ^{13}C NMR ($CDCl_3$): 14.0, 14.2, 40.1, 60.3, 69.7, 114.0, 120.5, 129.8, 158.3, 174.2. Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H: 7.74. Found: C, 69.73; H, 7.63.

4.1.2. Ethyl 2-methyl-3-(*p*-methoxyphenoxy)propanoate (2b). Colourless oil (2.90 g, 95%). IR (KBr): 2980, 1733, 1593, 1506, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.27 (m, 6H), 2.91 (sex, J=6.1 Hz, 1H), 3.76 (s, 3H), 3.94 (dd, J=9.1, 6.1 Hz, 1H), 4.17 (m, 3H), 6.82 (m, 4H). ^{13}C NMR: 13.9, 14.1, 39.9, 55.6, 60.5, 70.3, 114.5, 115.6, 152.7, 153.9, 174.3. Anal. calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.61. Found: C, 65.21; H, 7.56.

4.1.3. Ethyl 2-methyl-3-(*p*-chlorophenoxy)propanoate (2c). Colourless oil (3.92 g, 97%). IR (KBr): 2981, 1736, 1709, 1656, 1594, 1492 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.28 (m, 6H), 2.96 (sex, J=6.7 Hz, 1H), 3.89 (dd, J=9.2, 6.7 Hz, 1H), 4.18 (m, 3H), 6.75 (d, J=9.2 Hz, 2H), 7.23 (d, J=9.2 Hz, 2H). ^{13}C NMR: 14.0, 14.1, 39.8, 60.3, 69.8, 115.8, 125.8, 128.8, 157.7, 174.2. Anal. calcd for $C_{12}H_{16}O_3Cl$: C, 66.09; H, 6.82. Found: C, 65.75; H, 6.77.

4.1.4. Ethyl 2-methyl-3-(*p*-tertiobutylphenoxy)propanoate (2d). Yellow oil (3.20 g, 90%). IR (KBr): 2963; 1737; 1610; 1514; 1465 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.27 (m, 15H), 2.92 (sex, J=6.4 Hz, 1H), 3,99 (dd, J=8.8, 6.4 Hz, 1H), 4.17 (m, 3H), 6.95 (d, J=8.7 Hz, 2H), 7.2 (d, J=8.7 Hz, 2H). ^{13}C NMR: 14.0, 14.2, 31.5, 34.0, 39.9, 60.6, 69.6, 114.1, 126.6, 143.6, 156.4, 174.3. Anal. calcd for $C_{16}H_{24}O_3$: C, 72.79; H, 9.15. Found: C, 72.56; H, 9.03.

4.1.5. Ethyl 2-methyl-3-(*m*-methoxyphenoxy)propanoate (2e). Colourless oil (2.30 g, 77%). IR (KBr): 2980, 1735, 1603, 1493, 1467 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.28 (m, 6H), 3.00 (sex, J=6.2 Hz, 1H), 3.79 (s, 3H), 3.99 (dd, J=6.2, 4.1 Hz, 1H), 4.18 (m, 3H), 6.55 (m, 3H), 7.2 (t, 1H, J=8 Hz). ^{13}C NMR: 13.9, 14.1, 39.8, 55.2, 60.1, 69.5, 101.1, 106.6, 106.7, 129.8, 159.9, 160.7, 174.2. Anal. calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.61. Found: C, 65.48; H, 7.54.

4.1.6. Ethyl 2-methyl-3-(*o*-methoxyphenoxy)propanoate (2f). Colourless oil (3.21 g, 87%). IR (KBr): 2980, 1735, 1509, 1466 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (m, 6H), 3.02 (sex, J=6.9 Hz, 1H), 3.84 (s, 3H), 4.01 (dd, J=9.6, 6.9 Hz, 1H); 4.17 (q, J=6.9 Hz, 2H), 4.27 (dd, J=9.6, 6.9 Hz, 2H), 6.94–7.04 (m, 4H). ^{13}C NMR: 14.0, 14.1, 39.8, 55.9, 60.5, 70.9, 112.3, 114.5, 120.8, (CH); 121.6, 148.2, 149.8, 174.4. Anal. calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.61. Found: C, 65.44; H, 7.60.

4.2. Cyclisation reactions, general procedure

The ester **2** was dissolved either in MsOH or in toluene containing the acid. The reaction mixture was heated as indicated in Table 1; the solution was poured into a mixture of ice-cooled water, extracted with dichloromethane, washed with a saturated aqueous solution of $NaHCO_3$, brine and dried over $MgSO_4$. After solvent evaporation the residue was purified by flash chromatography leading to 3-methyl-4-chromanones **1a**–**f**.

Spectral data of **1a**,[7a] **1c**,[7a,8a] **1e**,[7b] **1f**,[33] are in accord with those of the literature.

4.2.1. 6-Methoxy-3-methyl-4-chromanone 1b. Yellow solid, mp=39°C, IR (KBr) 2974, 1690, 1617, 1490, 1456, 1429, 1270 cm^{-1}. ^{1}H NMR (250 MHz. $CDCl_3$) δ 1.21 (d, J=6.9 Hz, 3H), 2.82 (m, 1H), 3.79 (s, 3H), 4.10 (dd, J=11.2, 10.9 Hz, 1H), 4.45 (dd, J=11.1, 5.0 Hz, 1H), 6.88 (d, J=9.1 Hz, 1H), 7.07 (dd, J=9.1, 3.1 Hz, 1H), 7.31 (d, J=3.1 Hz, 1H). ^{13}C NMR (62 MHz. $CDCl_3$) δ 10.8, 40.6, 55.7, 72.3, 107.7, 119.0, 120.3, 124.8, 154.0, 156.4, 194.9. Anal. calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.58; H, 6. 09.

4.2.2. 6-*t*-Butyl-3-methyl-4-chromanone 1d. Yellow oil. IR (KBr) 2963, 1694, 1614, 1579, 1493 cm^{-1}. ^{1}H NMR (250 MHz. $CDCl_3$) δ 1.20 (d, J=7.2 Hz, 3H), 1.30 (s, 9H), 2.76 (m, 1H), 4.12 (t, J=11.1 Hz, 1H), 4.47 (dd, J=11.1, 5.0 Hz, 1H), 6.89 (d, J=8.1 Hz, 1H), 7.53 (dd, J=8.1, 2.7 Hz, 1H), 7.89 (d, J=2.7 Hz, 1H). ^{13}C NMR (62 MHz. $CDCl_3$) δ 10.9, 31.5, 34.2, 40.3, 72.1, 117.6, 119.7, 123.2,

129.7, 133.5, 159.9, 195.7. Anal. calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.26. Found: C, 76.85; H, 8.39.

4.3. Carboxybenzylation of compounds (1), general procedure[20]

A solution of lithium hexamethyldisilazane was prepared by slow addition of *n*-BuLi (1.6 M in hexane, 1.2 equiv.) to hexamethyldisilazane (1.2 equiv.) at −78°C in THF (1 mL per mmol) under argon. After 30 min of stirring, a THF solution (1 mL per mmol) of chromanone **1** (1 equiv.) was added dropwise during 20 min. After further 30 min of stirring the THF solution (0.3 mL per mmol) of benzylcyanoformate (1.2 equiv.) was added. The mixture was warmed to room temperature and the contents of the flask poured into 10% aqueous NH_4Cl. The aqueous phase was extracted three times with ether (0.5 mL per mmol). The combined organic phases were washed with brine and dried with $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 95:5) to afford pure **5**.

4.3.1. 3-Benzyloxycarbonyl-3-methylchroman-4-one (5a). Colourless oil (2.19 g, 60%). IR (KBr): 3034, 2938, 1737, 1697, 1608, 1478, 1465, 1311, 1282, 1221 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.48 (s, 3H), 4.22 (d, J=11.6 Hz, 1H), 4.83 (d, J=11.6 Hz, 1H), 5.11 (d, J=12.5 Hz, 1H), 5.22 (d, J=12.5 Hz; 1H), 6.96 (d, J=8.3 Hz, 1H), 7.06 (t, J=7.8 Hz, 1H); 7.15 (m, 2H), 7.28 (m, 3H), 7.49 (m, 1H), 7.95 (dd, J=8.3, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.9, 53.4, 67.2, 73.7, 117.8, 120.1, 121.8, 127.5, 127.8, 128.1, 128.4, 135.2, 136.0, 161.1, 170.4, 190.2. MS: 296 (M^+; 12), 162 (74), 120 (100).

4.3.2. 3-Benzyloxycarbonyl-6-methoxy-3-methylchroman-4-one (5b). White solid (2.02, 54%), Flash chromatography, petroleum ether/ethyl acetate, 90:10, mp=73°C. IR (KBr) 2942, 1739, 1679, 1611, 1578, 1259 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.47 (s; 3H), 3.80 (s, 3H); 4.17 (d, J=11.5 Hz, 1H); 4,77 (d, J=15.5 Hz; 1H), 5.10 (d, J=12.6 Hz, 1H); 5.22 (d, J=12.6 Hz, 1H); 6.89 (d, J=9.1 Hz, 1H), 6.87–7.19 (m, 3H), 7.28 (m, 3H), 7,35 (d, J=3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.9, 53.2, 55.7, 67.2, 73.8, 107.9, 119.0, 119.9, 125.2, 127.5, 128.1, 128.4, 135.2, 154.3, 155.7, 170.5, 190.2. Anal. calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.84; H, 5.61.

4.3.3. 3-Benzyloxycarbonyl-6-chloro-3-methylchroman-4-one (5c). White solid (3.1 g, 74%), mp=98°C. IR: 3069, 1721, 1694, 1604, 1477, 1460, 1419, 1231 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (s, 3H), 4.19 (d, J=11.9 Hz, 1H), 4.81 (d, J=11.9 Hz, 1H), 5.09 (d, J=12.3 Hz, 1H), 5.20 (d, J=12.3 Hz, 1H), 6.90 (d, J=8.8 Hz, 1H), 7.15 (m, 2H), 7.28 (m, 3H), 7.41 (ddd, J=8.8, 2.7, 0.7 Hz, 1H), 7.88 (d, J=2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.7, 53.1, 67.4, 73.8, 119.5, 120.9, 127.0, 127.3, 127.6, 128.2, 128.5, 135.0, 135.8, 159.4, 170.0, 189.0. Anal. calcd for $C_{18}H_{15}O_4Cl$: C, 65.63; H, 4.57. Found: C, 65.38; H, 4.52.

4.3.4. 3-Benzyloxycarbonyl-6-*t*-butyl-3-methylchroman-4-one (5d). White solid (1.86 g, 85%), mp=65°C. IR: 2956, 1730, 1699, 1616, 1495, 1298, 1263 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.31 (s, 9H), 1.48 (s, 3H), 4.19 (d, J=11.4 Hz, 2H), 4.80 (d, J=11.4 Hz, 2H), 5.10 (d, J=12.6 Hz, 2H), 5.23 (d, J=12.6 Hz, 2H), 6.90 (d, J=8.8 Hz, 1H), 7.15 (m, 2H), 7.26 (m, 3H), 7.55 (dd, J=8.8, 2.3 Hz, 1H), 7.93 (d, J=2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 16.0, 31.2, 34.3, 53.4, 67.2, 73.7, 117.4, 119.3, 123.7, 127.4, 128.1, 128.4, 133.8, 135.2, 144.8, 159.0, 170.6, 190.5. Anal. calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.46; H, 7.00.

4.3.5. 3-Benzyloxycarbonyl-7-methoxy-3-methylchroman-4-one (5e). White solid (1.50 g, 88%), Flash chromatography, petroleum ether/ethyl acetate, 90:10, mp=53°C. IR: 3004, 1728, 1492, 1460, 1430, 1228 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (s, 3H), 3.82 (s, 3H), 4.19 (d, J=11.5 Hz, 1H), 4.80 (d, J=11.5 Hz, 1H), 5.11 (d, J=12.6 Hz, 1H), 5.22 (d, J=12.6 Hz, 1H), 6.38 (d, J=2.6 Hz, 1H), 6.61 (dd, J=8.9, 2.3 Hz, 1H), 7.17 (m, 2H), 7.28 (m, 3H), 7.87 (d, J=8.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 16.0, 53.0, 55.6, 67.1, 73.9, 100.5, 110.5, 113.8, 127.5, 128.1, 128.3, 129.4, 135.3, 163.0, 166.0, 170.5, 188.7. Anal. calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.56; H, 5.52.

4.3.6. 3-Benzyloxycarbonyl-8-methoxy-3-methylchroman-4-one (5f). White solid (1.50 g, 92%), Flash chromatography, petroleum ether/ethyl acetate, 90:10, mp=82°C. IR: 2991, 1731, 1687, 1604, 1584, 1487, 1455, 1273, 1206 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.48 (s, 3H), 3.89(s, 3H), 4.28 (d, J=11.4 Hz, 2H), 4.91 (d, J=11.4 Hz, 2H), 5.10 (d, J=12.6 Hz, 2H), 5.22 (d, J=12.6 Hz, 2H), 7.04 (m, 2H), 7.17 (m, 2H), 7.29 (m, 3H), 7.54 (dd, J=7.6, 1.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.9, 53.3, 56.2, 67.2, 74.1, 116.7, 118.9, 120.7, 121.3, 127.6, 128.1, 128.4, 135.2, 148.5, 151.0, 170.2, 190.1. Anal. calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.05; H, 5.77.

4.3.7. General procedure for the deprotection, decarboxylation. To a round bottom flask containing a solution of **5** (100 mg) in the corresponding solvent (20 mL) were successively added the aminoalcohol (0.3 equiv.) and palladium on charcoal (0.025 equiv.). Gaseous hydrogen was supplied by a 'gas bag' or bubbled continuously through the solution until complete disappearance of starting material, as indicated by TLC (Tables 3–5). The crude mixture was filtered over a pad of silica and purified by chromatography. Yields are reported in Tables 3–5. Spectral data have been described above and CD spectra of each compound was similar to that of **1c** shown in Figure 5. For the optical rotation and HPLC analysis: **1a** $[\alpha]_D$=+20.8 (c=0.24, $CHCl_3$) [(*R*) 73% ee]; Regis (*S*,*S*) Whelk-O1 isopropanol/hexane 0.1:99.9; flow rate: 2 mL/min; retention time, (*S*) 14.6 min, (*R*) enantiomer: 16.7 min, α=1.17. **1b** $[\alpha]_D$=+105.7 (c=0.14, $CHCl_3$) [(*R*) 69% ee]; Regis (*S*,*S*) Whelk-O1 isopropanol/hexane 0.2:98.8; flow rate: 2 mL/min; retention time (*S*) 15.8 min, (*R*) 17.5 min, α=1.14. **1c** $[\alpha]_D$=+37.6 (c=0.24, $CHCl_3$) [(*R*) 60% ee]; Regis (*S*,*S*) Whelk-O1 isopropanol/hexane 0.1:99.9; flow rate: 2 mL/min; retention time (*S*) 9.5 min, (*R*) 11.1 min, α=1.24. **1d** $[\alpha]_D$=+27.7 (c=0.34, $CHCl_3$) [(*R*) 75% ee]; Regis (*S*,*S*) Whelk-O1 isopropanol/hexane 0.1:99.9; flow rate: 1.8 mL/min; retention time (*S*) 11.3 min, (*R*) 12.9 min, α=1.20. **1e** $[\alpha]_D$=+29 (c=0.20, $CHCl_3$) [(*R*) 64% ee]; Regis (*S*,*S*) Whelk-O1 isopropanol/hexane 0.8:99.2; flow

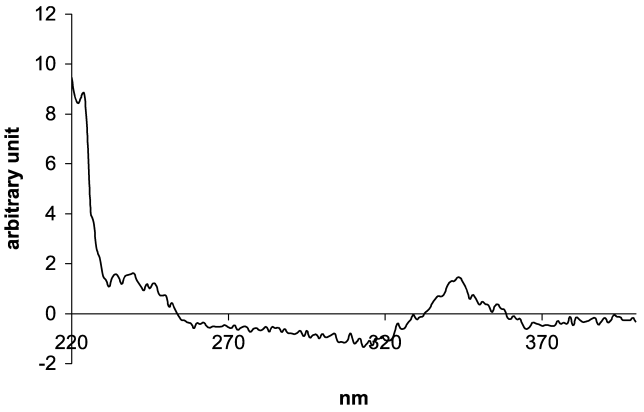


Figure 5. CD spectra of **1c** recorded in acetonitrile.

rate: 2 mL/min; retention time (*S*) 16.6 min, (*R*) 18.9 min, α=1.23. **1f** $[\alpha]_D$=+33.8 (c=0.42, $CHCl_3$) [(*R*) 69% ee]; Chiracel OD isopropanol/hexane 4:96; flow rate: 1 mL/min; retention time (*S*) 14.8 min, (*R*) 15.9 min, α=1.13.

Acknowledgements

We are grateful to the 'Ministère de la Recherche et de la Technologie' for a PhD studentship to O. R. and to Engelhard and Johnson Matthey Companies for the gift of Pd catalysts. We thank Isabel Mondim for a few experiments, Dr D. K. Mukherjee for help with the text of the manuscript, Professor A. Alix and G. Moroy (Reims University) for the facilities in recording CD spectra.

References

1. (a) Adinolfi, M.; Aquila, T.; Barone, G.; Lanzetta, R.; Parrilli, M. *Phytochemistry* **1989**, *28*, 3244–3246. (b) Corsaro, M. M.; Lanzetta, R.; Mancino, A.; Parrilli, M. *Phytochemistry* **1992**, *31*, 1395–1397.
2. Wall, M. E.; Wani, M. C.; Manikumar, G.; Taylor, H.; McGivney, R. *J. Nat. Prod.* **1989**, *52*, 774–778.
3. Della Loggia, R.; Del Negro, P.; Tubaro, A.; Barone, G.; Parrilli, M. *Planta Med.* **1989**, *55*, 587–588.
4. Muzart, J.; Hénin, F.; Jamal Aboulhoda, S. *Tetrahedron: Asymmetry* **1997**, *8*, 381–389.
5. (a) Roy, O.; Diekmann, M.; Riahi, A.; Hénin, F.; Muzart, J. *Chem. Commun.* **2001**, 533–534, see also: p 1418. (b) Roy, O.; Riahi, A.; Hénin, F.; Muzart, J. *Eur. J. Org. Chem.* **2002**, 3986–3994.
6. Direct alkylation of chromanones: (a) Al Nakib, T.; Bezjak, V.; Meegan, M. J.; Chandy, R. *Eur. J. Med. Chem.* **1990**, *25*, 455–462. (b) Santhosh, K. C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 7727–7730. (c) Mandal, P.; Venkateswaran, R. V. *J. Chem. Res. (S)* **1998**, 88–89.
7. From o-substituted phenols: (a) Barlocco, D.; Cignarella, G.; Curzu, M.; M, . *Synthesis* **1985**, 876–878. (b) Jain, A. C.; Tyagi, O. D.; Saksena, R. *Indian J. Chem.* **1989**, 15–20. (c) Valenti, P.; Belluti, F.; Rampa, A.; Bisi, A. *Synth. Commun.* **1999**, *29*, 3895–3899. (d) Draper, R. W.; Hu, B.; Iyer, R. V.; Li, X.; Lu, Y.; Rahman, M.; Vater, E. J. *Tetrahedron* **2000**, *56*, 1811–1817.
8. Friedel–Crafts type cyclisation from carboxylic acids, acyl chlorides or nitriles: (a) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commun.* **1998**, 1639–1640. (b) Loubinoux, B.; Colin, J.-L.; Antonot-Colin, B. *Tetrahedron* **1987**, *43*, 93–100. (c) Narkhede, D. D.; Iyer, P. R.; Iyer, C. S. R. *Tetrahedron* **1990**, *46*, 2031–2034. (d) Srikanth, N.; Kon, O.-L.; Ng, S.-C.; Sim, K.-Y. *J. Chem. Res. (S)* **1997**, 202–203.
9. Lipinski, C. A.; Aldinger, C. E.; Beyer, T. A.; Bordner, J.; Burdi, D. F.; Bussolotti, D. L.; Inskeep, P. B.; Siegel, T. W. *J. Med. Chem.* **1992**, *35*, 2169–2177.
10. Cyclocarbonylation of iodophenols: (a) Okuro, K.; Alper, H. *J. Org. Chem.* **1997**, *62*, 1566–1567. (b) Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7125–7128.
11. (a) Loiodice, F.; Longo, A.; Bianco, P.; Tortorella, V. *Tetrahedron: Asymmetry* **1995**, *6*, 1001–1011. (b) Woydowski, K.; Liebscher, J. *Synthesis* **2000**, 1444–1448. (c) Tanada, Y.; Mori, K. *Eur. J. Org. Chem.* **2001**, 1963–1966.
12. (a) Vicario, J. L.; Badia, D.; Dominguez, E.; Rodriguez, M.; Carrillo, L. *Tetrahedron Lett.* **2000**, *41*, 8297–8300. (b) Vicario, J. L.; Badia, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2003**, *14*, 489–495.
13. Loubinoux, B.; Viriot-Chauveau, C.; Sinnes, J. L. *Tetrahedron Lett.* **1992**, *33*, 2145–2148.
14. (a) Davis, F. A.; Chen, B.-C. *J. Org. Chem.* **1993**, *58*, 1751–1753. (b) Woydowski, K.; Ziemer, B.; Liebscher, J. *J. Org. Chem.* **1999**, *64*, 3489–3491. (c) Hansen, K. B.; Rabbat, P.; Springfield, S. A.; Devine, P. N.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 8743–8745.
15. (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299. (b) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899–1902.
16. Roy, O.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron* **2000**, *56*, 8133–8140.
17. (a) Gopalan, B.; Rajagopalan, K.; Sunitha, K.; Balasubramanian, K. K. *Tetrahedron* **1985**, *41*, 3153–3159. (b) Barton, D. H. R.; Fekih, A.; Lusinchi, X. *Bull. Soc. Chim. Fr.* **1988**, 681–687. (c) Drewes, S. E.; Emslie, N. D.; Karodia, N.; Loizou, G. *Synth. Commun.* **1990**, *20*, 1437–1443.
18. Marquié, J.; Laporte, C.; Laporterie, A.; Dubac, J.; Desmurs, J.-R.; Roques, N. *Ind. Eng. Chem. Res.* **2000**, *39*, 1124–1131.
19. Such a splitting of a *t*-Bu substituent under Friedel–Crafts conditions is known: Tashiro, M. *Synthesis* **1979**, 921–936.
20. Donnelly, D.; Finet, J.-P.; Rattigan, B. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1729–1735.
21. Jamal Aboulhoda, S.; Létinois, S.; Wilken, J.; Reiners, I.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1865–1868.
22. *Heterogeneous Catalysis for the Synthetic Chemist*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1996; Chapters, 2, 3, 9.
23. Review: (a) Blaser, H.-U.; Jalett, H.-P.; Müller, M.; Studer, M. *Catal. Today* **1997**, *37*, 441–463. Recent examples: (b) LeBlond, C.; Wang, J.; Liu, J.; Andrews, A. T.; Sun, Y.-K. *J. Am. Chem. Soc.* **1999**, *121*, 4920–4921. (c) Blaser, H.-U.; Jalett, H.-P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, *122*, 12675–12686. (d) Ferri, D.; Bürgi, T.; Baiker, A. *J. Chem. Soc., Chem. Commun.* **2001**, 1172–1173. (e) Kubota, J.; Zaera, F. *J. Am. Chem. Soc.* **2001**, *123*, 11115–11116.

24. (a) Nitta, Y.; Kubota, T.; Okamoto, Y. *Bull. Soc. Chim. Jpn* **2001**, *74*, 2161–2165. (b) Farkas, G.; Sıpos, Ė.; Tungler, A.; Sárkány, A.; Figueiredo, J. L. *J. Mol. Catal. A: Chem.* **2001**, *170*, 101–107.
25. Farkas, G.; Hegedűs, L.; Tungler, A.; Máthé, T.; Figueiredo, J. L.; Freitas, M. *J. Mol. Catal. A: Chem.* **2000**, *153*, 215–219.
26. This observation was justified by comparison of the results starting from **5c/7a** in presence of palladium on charcoal and black palladium (Table 3, entry 10 and Table 5, entry 3, respectively).
27. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
28. A remarkable effect of the *para*-methoxy group has already been observed for an Hammett correlation,[29] as an out position of the corresponding point.[30]
29. Wiegers, A.; Scharf, H.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 2303–2312.
30. List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.
31. Duhamel, L.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1982**, *II*, 75–83.
32. (a) Landis, C.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746–1754. (b) Balázsik, K.; Szöri, K.; Felföldi, K.; Török, B.; Bartók, M. *Chem. Commun.* **2000**, 555–556. (c) Von Arx, M.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3089–3094. (d) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002–8003. (e) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605–3614.
33. Engler, T. A.; LaTessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755–1769.