Tetrahedron 66 (2010) 3024–3029

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Asymmetric Friedel–Crafts alkylation of activated benzenes with methyl (*E*)-2-oxo-4-aryl-3-butenoates catalyzed by [Pybox/Sc(OTf)$_3$]

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ARTICLE INFO

Article history:
Received 19 November 2009
Received in revised form 22 January 2010
Accepted 15 February 2010
Available online 18 February 2010

Keywords:
Asymmetric catalysis
Friedel–Crafts reaction
Enantioselectivity
PYBOX ligand
Scandium triflate

ABSTRACT

The asymmetric Friedel–Crafts reaction between methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a–c**) and activated benzenes (**2a–d**) has been efficiently catalyzed by the Sc^{III} triflate complex of (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl) oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (pybox **3**). The 4,4-diaryl-2-oxo-butyric acid methyl esters (**4**) are usually formed in good yields and the enantioselectivity is up to 99% ee. The sense of the stereoinduction can be rationalized with the same octahedral complex (**10**) between **1**, pybox **3** and Sc triflate already proposed for other reactions involving pyruvates, and catalyzed by the same complex.

1. Introduction

The catalytic enantioselective Friedel–Crafts reaction involving the formation of a new C–C bond between a double bond and an activated aromatic ring is one of the most fundamental and flexible reactions in organic chemistry.[1]

Indole is the most frequently used aromatic ring because of the biological relevance of its reaction products;[2–18] some selected examples show that the reaction may occur: (a) with an electron-poor alkene, which is usually an activated α,β-unsaturated carbonyl compound such as aryliden-pyruvates,[1d–5a,b] ethene-di- and tri-carboxylates,[6–9] α,β-unsaturated acyl phosphonates,[5c,d,10] nitroalkenes,[11–13] α′-hydroxy-enones,[14] simple enones;[15] (b) on the carbon atom of a carbonyl group following the scheme of an aldol reaction;[16,17] (c) on the carbon atom of an imino group to give an aromatic amine.[18]

The Friedel–Crafts reaction involving activated benzenes is less common, but again the reaction with α-imino esters has been used to obtain non-natural aromatic α-amino acids,[19] as in the alkylation of ethyl trifluoropyruvate to synthesize aromatic α-hydroxy-esters.[16,20–23]

With such wide research around this topic, it seems rather astonishing that only two examples of enantioselective reactions with activated benzenes have been reported. The reaction between 1,3-dimethoxybenzene and methyl 4-phenyl-2-oxo-3-butenoate or ethyl 2-oxo-3-pentenoate, catalyzed by [(4′*S*)-2,2-bis[4′-phenyl-1′,3′-oxazolin-2′-yl]propane/Cu(OTf)$_2$] (Ph-Box) complex, has been studied, and the enantioselectivity was 60 and 89% ee, respectively.[2] The enantioselective organocatalytic 1,4-addition of α,β-unsaturated aldehydes and several aromatic amines has been reported to give the alkylated products with ee in the range 84–99%.[24]

The successful metal-catalyzed asymmetric addition of aromatic derivatives to alkenes requires the synergistic concurrence of two elements: an electron-rich benzene, and a suitably designed catalyst based on a Lewis acid and a chiral ligand, which is usually a Cu^{II}/Box complex,[1a,25] or a [lanthanide/2,6-bis(4′-1′,3′-oxazolin-2′-yl)pyridine (pybox) complex.[1a,26]

Since our previous research focussed on methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a–c**), which react either with cyclopentadiene to give a Diels–Alder reaction,[27] or with indole in the above mentioned Friedel–Crafts reaction,[4] with excellent yield and enantioselectivity when catalyzed with the Sc^{III} triflate complex of (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl] pyridine (**3**) (TIPS-pybox), the reaction between **1a–c** and some electron-rich benzenes was tested under the same catalytic conditions. The choice of **1a–c** was also determined from the results of the above research.[4,27] These unsaturated α-dicarbonyl compounds bind to the catalyst as a bicoordinating reagent, and the resulting reactive intermediate suggests a defined approach, which is interesting to test if it corresponds to the experimental stereochemical result.

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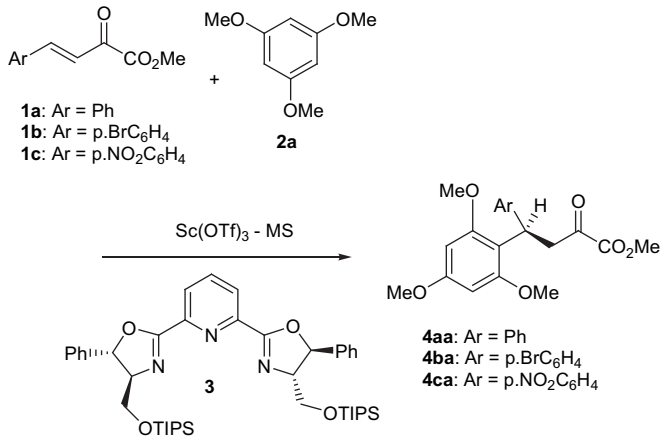
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.02.054

2. Results and discussion

The first simple model to test the efficiency of the catalyst was the reaction of **1** with 1,3,5-trimethoxybenzene (**2a**). Preliminarily, the reaction of methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**1a**) and **2a** was performed with Sc^{III} triflate in the absence of a chiral ligand in CH_2Cl_2 at −50 °C (Scheme 1), and the yield of **4aa** was nearly quantitative (Table 1—entry 1). Then, the same reaction was run both at −50 °C and −20 °C with 10% mol of [(TIPS-pybox)/$Sc(OTf)_3$] and 3 Å molecular sieves (MS), the main difference being simply the time required to consume the starting materials.



Scheme 1. Reaction of methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a**–**c**) with 1,3,5-trimethoxybenzene (**2a**).

The structure of **4aa** was easily determined by ^1H- and ^{13}C NMR spectroscopy and IR analysis of the product isolated after simple column chromatographic separation of the reaction product from **3**. The yield was excellent and the ee at −50 °C and −20 °C, determined by HPLC on Chiralpak AD column, was 97 and 99%, respectively (Table 1—entries 2,3).

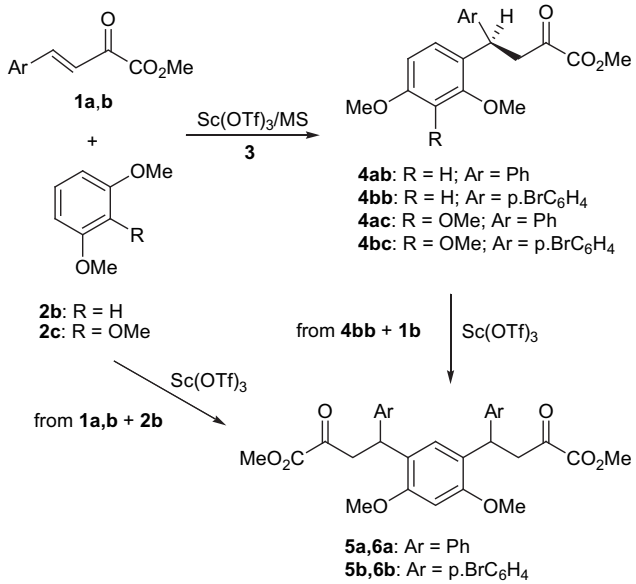
Under the same conditions, the reactions between methyl (*E*)-2-oxo-4-(4-bromophenyl)-3-butenoate and the 4-nitro-analogue (**1b**,**c**) and **2a** were performed with catalyst based on either Sc^{III} (Table 1—entries 4,7) or [(**3**)/$Sc(OTf)_3$] (Table 1—entries 5,6,8,9). Even if the reactions at −50 °C give low yields (56 and 20% for **1b** and **1c**, respectively), the enantioselectivities are again excellent (ee >95%). At −20 °C the ee are slightly lowered (87–89%), but the yields are significantly higher.

Table 1
Friedel–Crafts reaction between methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a**–**c**) and **2a** in CH_2Cl_2 at −50 °C catalyzed by 10 mol % catalyst

Entry	Reagent	Catalyst	T/°C	Time	Product	**4** Yield %	**4** ee %
1	**1a**	$Sc(OTf)_3$	−50	1 h	**4aa**	90	—
2	**1a**	[**3**/$Sc(OTf)_3$]	−50	24 h	**4aa**	92	97 (+)
3	**1a**	[**3**/$Sc(OTf)_3$]	−20	5 h	**4aa**	97	>99 (+)
4	**1b**	$Sc(OTf)_3$	−50	1 h	**4ba**	70	—
5	**1b**	[**3**/$Sc(OTf)_3$]	−50	24 h	**4ba**	56	99 (+)
6	**1b**	[**3**/$Sc(OTf)_3$]	−20	7 h	**4ba**	86	89 (+)
7	**1c**	$Sc(OTf)_3$	−20	2 h	**4ca**	84	—
8	**1c**	[**3**/$Sc(OTf)_3$]	−50	7 days	**4ca**	20	96 (+)
9	**1c**	[**3**/$Sc(OTf)_3$]	−20	2 days	**4ca**	85	87 (+)

The Friedel–Crafts reaction was performed on two further methoxybenzenes: 1,3-dimethoxybenzene (**2b**), already tested in the reaction with **1a** catalyzed by [(Ph-box)/$Cu(OTf)_2$],[2] and 1,2,3-trimethoxybenzene (**2c**).

Sc^{III} catalysis of the reaction between **1a**,**b** (the reaction with **1c** is sluggish at ambient temperature) and **2b** at −20 °C gave two main products: **4ab**, a product already described by Jørgensen,[2] and its analogue **4bb**, both of which are the result of the electrophilic attack in the most activated 4-position of **2b**. These reactions gave two further couples of diastereomeric products: **5a** and **6a** from **2a** (difficult to isolate but clearly detected by ^1H- and ^{13}C NMR spectroscopy), **5b** and **6b** from **2b**, separated by column chromatography. These [1:2] products derive from a further electrophilic attack of **1a** and **1b** on the activated 5-position of **4ab** and **4bb** (Scheme 2—Table 2: entries 1,3). This was experimentally proved running the reaction between **1b** and **4bb**, which gave **5b** and **6b** (Scheme 2).



Scheme 2. Reactions between methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a**,**b**) and 1,3-dimethoxy- or 1,2,3-trimethoxybenzenes (**2b**,**c**).

The above reactions were then performed with [(**3**)/$Sc(OTf)_3$] as catalyst at ambient temperature between **1a** and **2b**, and at −20 °C between **1b** and **2b**. Under these conditions, the bis-addition is suppressed and the only products obtained are **4ab** and **4bb**.The rate of the reactions are lowered, the yields are modest (probably because of the less Lewis-acid character of Sc^{III} after the coordination with **3**), but the ee of **4ab** (93%) and **4bb** (80%) are again satisfactory and even better than some results reported in the literature (Table 2—entries 2,4). The reaction between 1,2,3-trimethoxybenzene (**2c**) and **1a**,**b**, catalyzed by $Sc(OTf)_3$ is sluggish and must be performed at ambient temperature. The yields are satisfactory and the attack of the electrophiles occurs in the 4-position to give **4ac** and **4bc** (Scheme 2, Table 2—entries 5,6). Unfortunately, the same reactions, performed with [(**3**)/$Sc(OTf)_3$] as catalyst, do not give significant amount of products.

The reaction between **1a**,**b** and 3-methoxy-*N*,*N*-dimethylaniline (**2d**), performed with $Sc(OTf)_3$, gave **4ad** and **4bd** as main products, resulting from the attack of the electrophiles in the most activated 4-position of **2d**. The reaction of **1a** also gave a couple of diastereoisomers **7** and **8**, separated by column chromatography, whose ^1H- and ^{13}C NMR spectra show they derive from the intermediate **9**, which can either collapse to **4ad**, or can be quenched by a second molecule of **1a** (Scheme 3).

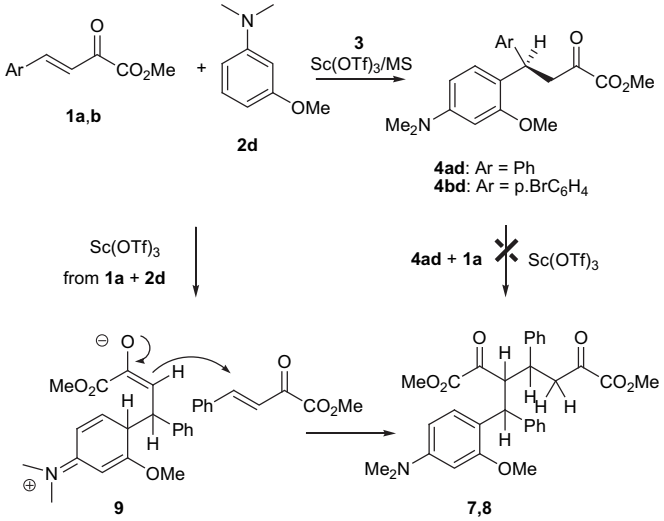
The main difference from the reactivity reported in Scheme 2 is that, in this case, **7** and **8** cannot be obtained from **4ad**. No by-product was obtained in a detectable yield from **1b**.

When the reactions were performed at −20 °C with [(**3**)/$Sc(OTf)_3$] as catalyst, the bis-addition is suppressed, **4ad** and **4bd** are the only reaction products (Scheme 3, Table 3—entries 2,4), the yields are good and the enantiomeric excess is higher than 90%.

Table 2
Friedel–Crafts reaction in CH_2Cl_2 between methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a**,**b**) and 1,3,-dimethoxybenzene (**2b**) (at −20 °C) or 1,2,3-trimethoxybenzene (**2c**) (at ambient temperature) catalyzed by 10 mol % catalyst

Entry	1	2	Catalyst	T/°C	Time	Product	4 Yield %	4 ee %	Config.
1	**1a**	**2b**	$Sc(OTf)_3$	−20	24 h	**4ab**[a]	57	—	
2	**1a**	**2b**	[**3**/$Sc(OTf)_3$][b]	t.a.	24 h	**4ab**	65	93 (+)	(4*R*)
3	**1b**	**2b**	$Sc(OTf)_3$	−20	12 h	**4bb**[c]	42	—	
4	**1b**	**2b**	[**3**/$Sc(OTf)_3$]	−20	2 days	**4bb**	30	80 (+)	
5	**1a**	**2c**	$Sc(OTf)_3$	t.a.	48 h	**4ac**	64	—	
6	**1b**	**2c**	$Sc(OTf)_3$	t.a.	24 h	**4bc**	52	—	

[a] In addition 29% yield of a mixture of **5a** and **6a**.
[b] Catalyst: 20 mol %.
[c] In addition 8% yield of **5b** and 7% of **6b**.



Scheme 3. Reaction of methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a**,**b**) with 3-methoxy-*N*,*N*-dimethylaniline (**2d**).

Table 3
Friedel–Crafts reaction between methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a**,**b**) and 3-methoxy-*N*,*N*-dimethylaniline (**2d**) in CH_2Cl_2 at −20 °C catalyzed by 10 mol % catalyst

Entry	Reagent	Catalyst	T/°C	Time (h)	Product	4 Yield %	4 ee %
1	**1a**	$Sc(OTf)_3$	−20	2	**4ad**[a]	69	—
2	**1a**	[**3**/$Sc(OTf)_3$]	−20	4	**4ad**	70	92 (+)
3	**1b**	$Sc(OTf)_3$	−20	2	**4bd**	82	—
4	**1b**	[**3**/$Sc(OTf)_3$]	−20	10	**4bd**	83	93 (+)

[a] In addition 20% yield of **8** and 5% of **9**.

Based on the absolute configuration determined by X-ray analysis of a chiral Friedel–Crafts adduct formed under enantioselective catalysis with [(Ph-Box)/$Cu(OTf)_2$], the (*R*) configuration was assigned to the (+)-**4ab** product.[2] This is the same enantiomer obtained from the reaction between **1a** and **2b** catalyzed by [(**3**)/$Sc(OTf)_3$] (Table 2—entry 2). Hence it seems reasonable to assign the same absolute configuration to the major enantiomers obtained under these catalytic conditions.

The (*R*) configuration for the products of the Friedel–Crafts reaction between **1a**–**c** and the activated benzenes **2a**–**d** is consistent with an octahedral reacting intermediate (**10**), obtained by a bidentate coordination of **1a**–**c** to the Sc^{III} complex of **3** with the ketonic C=O group equatorial, the ester carbonyl in the axial position and a triflate ion or a water molecule axial, which undergoes the sterically less demanding attack of substituted benzenes to the (*Re*)-face of the coordinated electrophile (Fig. 1) to give (*R*)-products.

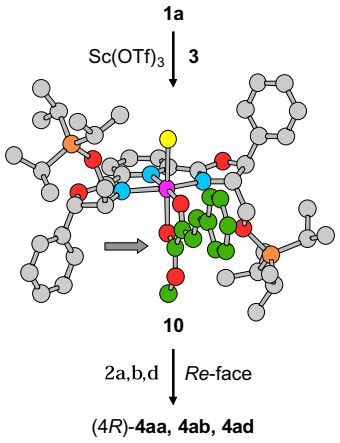


Figure 1. The assumed reacting intermediate **10** of the Friedel–Crafts alkylation reaction between **1a** and activated benzenes **2**, catalyzed by the $Sc(OTf)_3$ complex of pybox **3**, which gives the (*R*)-products.

3. Conclusion

In conclusion, this research deals with the asymmetric Friedel–Crafts reaction between methyl (*E*)-2-oxo-4-aryl-3-butenoates (**1a**–**c**) and activated benzenes (**2a**–**d**) catalyzed by the Sc^{III} triflate complex of (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl) oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (pybox **3**). The 4,4-diaryl-2-oxo-butyric acid methyl esters (**4**), which are usually formed in good yields and the enantioselectivity up to 99% ee, have the absolute configuration (*R*), whose formation can be rationalized with the octahedral intermediate (**10**).

Intermediate **10** has already been proposed to rationalize the sense of the stereoinduction of the Friedel–Crafts alkylation of indole with **1**,[4] the Diels–Alder/Hetero-Diels–Alder reactions of cyclopentadiene,[27] and the Mukaiyama–aldol reaction of pyruvates.[28]

The constancy of the model of the reacting intermediate in so many different reactions is a good index of the flexibility of the catalyst derived by pybox **3**, and offers promising perspectives to predict the stereoinduction in new reactions involving dicarbonyl derivatives.

4. Experimental section

4.1. General and material

Melting points were determined by the capillary method and are uncorrected. ^1H- and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively ($CDCl_3$, 25 °C, TMS). IR spectra were registered on a Perkin-Elmer RX I spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Separation and

purification of the products was carried out by column chromatography using Merck silica gel 60 (230–400 mesh). The enantiomeric excess (ee) of the products was determined by HPLC using Daicel columns (see text). Dichloromethane was hydrocarbon-stabilised Aldrich ACS grade, distilled from calcium hydride and used immediately. Scandium triflate was the Aldrich ACS reagent; powdered molecular sieves 3 Å were heated under vacuum at 300 °C for 5 h and kept in sealed vials in a dryer. (4′*S*,5′*S*)-2,6-Bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**3**) was prepared as previously described.[29] (*E*)-2-Oxo-4-phenyl-but-3-enoic acid methyl ester (**1a**) was prepared, following the literature method,[30,31] from etherification with methanol of the potassium salt, obtained from benzaldehyde and pyruvic acid in the presence of KOH: yellow needles from diisopropyl ether, mp 69–70 °C (lit.,[31] mp 70–71 °C). Following the same procedure, and starting from the suitable aldehyde, the following products were prepared: (*E*)-2-Oxo-4-(4-bromophenyl)-but-3-enoic acid methyl ester (**1b**), yield 35%, yellow needles from methanol, mp 120 °C (lit.,[32] mp 122 °C); (*E*)-2-oxo-4-(4-nitrophenyl)-but-3-enoic acid methyl ester (**1c**), yield 32%, bright orange crystals from ethyl acetate, mp 182–183 °C (lit.,[33] mp 182.5–183.5 °C).

4.2. Reaction between (*E*)-2-oxo-4-arylbut-3-enoic acid methyl ester (1a–c) and arenes (2a–d)

4.2.1. Reaction catalyzed by scandium triflate. General procedure. A mixture of (*E*)-2-oxo-4-arylbut-3-enoic acid methyl ester (**1a–c**) (0.30 mmol) and scandium triflate (0.03 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was stirred for 15 min at ambient temperature in a rubber septum sealed vial and then cooled at the temperature reported in Table 1. The required arene (**2a–d**) (0.40 mmol) was added (when liquid with a microsyringe) and stirring was continued at the temperature and for the time reported in Tables 1–3. The reaction was decomposed in water, extracted with CH_2Cl_2, dried, and the reaction mixture was separated by column chromatography (silicagel, 30 cm length, 1.5 cm diameter).

*4.2.2. Methyl 4-(2,4,6-trimethoxyphenyl)-2-oxo-4-phenylbutano-ate (**4aa**).* Eluant: cyclohexane/ethyl acetate 85:15, soft white needles, mp 56–57 °C (methanol/diisopropyl ether/hexane); [Found: C, 67.1; H, 6.1. $C_{20}H_{22}O_6$ requires C, 67.03; H, 6.19%]; ν_{max} (Nujol mull) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.31–7.12 (5H, m, Ph aromatic protons), 6.12 (2H, s, H3 and H5 aromatic proton), 5.16 (1H, t, *J* 8.1 Hz, benzylic proton), 3.82 (3H, s, O*Me*), 3.81 (1H, dd, *J* 17.6, 7.7 Hz, C*H*H), 3.79 (3H, s, O*Me*), 3.76 (6H, s, 2 O*Me*), 3.73 (1H, dd, *J* 17.6, 7.7 Hz, CH*H*); δ_C (75 MHz $CDCl_3$) 193.1, 161.2, 159.6, 158.4, 143.3, 127.4, 127.0, 125.2, 111.1, 90.6, 55.1, 54.7, 52.2, 42.4, 33.8.

*4.2.3. Methyl 4-(4-bromophenyl)-4-(2,4,6-trimethoxyphenyl)-2-oxobutanoate (**4ba**).* Eluant: cyclohexane/ethyl acetate 85:15, colourless oil; [Found: C, 55.1; H, 4.9. $C_{20}H_{21}BrO_6$ requires C, 54.93; H, 4.84%]; ν_{max} (liquid film) 1731 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.34 (2H, d, *J* 8.4 Hz, *ortho*-Br aromatic protons), 7.16 (2H, d, *J* 8.4 Hz, *meta*-Br aromatic protons), 6.10 (2H, s, H3 and H5 aromatic proton), 4.89 (1H, t, *J* 7.5 Hz, benzylic proton), 3.82 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.76 (6H, s, 2 O*Me*), 3.71 (2H, d, *J* 8.1 Hz, CH_2); δ_C (75 MHz $CDCl_3$) 192.7, 159.7, 158.3, 142.3, 130.4, 128.8, 118.9, 110.6, 90.6, 55.1, 54.7, 52.3, 42.1, 33.3.

*4.2.4. Methyl 4-(2,4,6-trimethoxyphenyl)-4-(4-nitrophenyl)-2-oxobutanoate (**4ca**).* Eluant: cyclohexane/ethyl acetate 85:15, light yellow oil; [Found: C, 59.6; H, 5.3; N, 3.3. $C_{20}H_{21}NO_8$ requires C, 59.55; H, 5.25; N, 3.47%]; ν_{max} (liquid film) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 8.08 (2H, d, *J* 8.5 Hz, *ortho*-nitro aromatic protons), 7.42 (2H, d, *J* 8.5 Hz, *meta*-nitro aromatic protons), 6.11 (2H, s, H3 and H5 aromatic proton), 5.29 (1H, t, *J* 7.6 Hz, benzylic proton), 3.91 (1H, dd, *J* 17.7, 7.6 Hz, C*H*H), 3.84 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.77 (6H, s, 2 O*Me*), 3.69 (1H, dd, *J* 17.7 Hz, 7.6 Hz, CH*H*); δ_C (75 MHz $CDCl_3$) 192.3, 160.9, 160.1, 158.2, 151.2, 145.5, 127.7, 127.4, 122.7, 109.8, 90.5, 55.1, 54.8, 52.4, 41.6, 33.6.

*4.2.5. Methyl 4-(2,4-dimethoxyphenyl)-2-oxo-4-phenylbutanoate (**4ab**).* Eluant: cyclohexane/ethyl acetate 80:20, colourless oil; ν_{max} (liquid film) 1730 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.23–7.31 (4H, m, aromatic protons), 7.20 (1H, m, aromatic proton), 6.99 (1H, d, *J* 9.0 Hz, H6 aromatic proton), 6.41–6.45 (2H, m, H3 and H5 aromatic protons), 4.96 (1H, t, *J* 7.6 Hz, benzylic proton), 3.84 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 3.77 (3H, s, O*Me*), 3.64 (1H, dd, *J* 16.8, 7.6 Hz, C*H*H), 3.49 (1H, dd, *J* 16.8, 7.7 Hz, CH*H*); δ_C (75 MHz $CDCl_3$) 192.4, 161.2, 159.5, 157.5, 143.0, 128.5, 128.3, 128.1 127.8, 127.7, 126.2, 123.9, 104.1, 98.7, 55.2, 52.8, 44.5, 38.6. These NMR spectra are identical to those reported in the literature.[2]

*4.2.6. Methyl 4-[5-(3-methoxycarbonyl-3-oxo-1-phenylpropyl)-2,4-dimethoxyphenyl]-2-oxo-4-phenylbutanoate (**5a** and **6a**).* Eluant: cyclohexane/ethyl acetate 80:20, thick colourless oil; ν_{max} (Nujol mull) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) (mixture of diastereoisomers) 7.30–7.16 (10H+10H, m, aromatic protons), 6.86 and 6.81 (2H, s+s, H6 of both diastereoisomer), 6.37 and 6.36 (2H, s+s, H3 of both diastereoisomer), 4.89 (1H, t, *J* 7.6 Hz, benzylic proton of one diastereoisomer), 4.88 (1H, t, *J* 7.6 Hz, benzylic proton of one diastereoisomer), 3.81 (3H+3H, s, 2 O*Me* of one diastereoisomer), 3.78 (3H+3H, s, 2 O*Me* of one diastereoisomer), 3.76 (3H+3H+3H+3H, s, 4 O*Me*), 3.54–3.46 (4H+4H, m, CH_2); δ_C (75 MHz $CDCl_3$) 192.5, 192.3, 161.2, 161.1, 156.27, 156.25, 142.9, 142.8, 128.6, 128.21, 128.19, 127.9, 127.7, 127.6, 126.2, 125.9, 122.9, 95.5, 55.4, 52.7, 44.3, 38.9, 38.8.

*4.2.7. Methyl 4-(4-bromophenyl)-4-(2,4-dimethoxyphenyl)-2-oxo-butanoate (**4bb**).* Eluant: cyclohexane/ethyl acetate 90:10, colourless oil; [Found: C, 55.9; H, 4.8. $C_{19}H_{19}BrO_5$ requires C, 56.03; H, 4.70%]; ν_{max} (liquid film) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.39 (2H, d, *J* 8.4 Hz, *ortho*-Br aromatic protons), 7.14 (2H, d, *J* 8.4 Hz, *meta*-Br aromatic protons), 6.98 (1H, d, *J* 9.1 Hz, H6 aromatic proton), 6.43 (2H, m, H3 and H5 aromatic proton), 4.89 (1H, t, *J* 7.5 Hz, benzylic proton), 3.84 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.76 (3H, s, O*Me*), 3.61 (1H, dd, *J* 17.2, 7.9 Hz, C*H*H), 3.48 (1H, dd, *J* 17.2, 7.3 Hz, CH*H*); δ_C (75 MHz $CDCl_3$) 193.7, 160.7, 159.3, 157.1, 141.7, 130.9, 129.2, 127.9, 122.9, 119.6, 103.7, 98.3, 55.1, 54.7, 54.8, 52.5, 43.7 37.8.

*4.2.8. Methyl 4-[5-(3-methoxycarbonyl-3-oxo-1-(4-bromophenyl) propyl)-2,4-dimethoxyphenyl]-2-oxo-4-(4-bromophenyl) butanoate (**5b**).* Elution with cyclohexane/ethyl acetate 85:15, after **4bb**, gave **5b** as thick colourless oil; [Found: C, 53.3; H, 4.28. $C_{30}H_{28}Br_2O_8$ requires C, 53.27; H 4.17%]; ν_{max} (Nujol mull) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.39 (4H, d, *J* 8.4 Hz, *orto*-Br aromatic protons), 7.05 (4H, d, *J* 8.4 Hz, *meta*-Br aromatic protons), 6.72 (1H, s, H6), 6.36 (1H, s, H3), 4.81 (2H, t, *J* 7.6 Hz, benzylic proton), 3.84 (6H, s, 2 O*Me*), 3.76 (6H, s, 2 O*Me*), 3.47 (4H, d, *J* 7.6 Hz, $2CH_2$); δ_C (75 MHz $CDCl_3$) 191.6, 160.7, 156.0, 141.4, 130.9, 129.1, 126.9, 121.8, 119.6, 95.1, 55.0, 52.5, 43.5, 38.0.

*4.2.9. Methyl 4-[5-(3-methoxycarbonyl-3-oxo-1-(4-bromophenyl) propyl)-2,4-dimethoxyphenyl]-2-oxo-4-(4-bromophenyl) butanoate (**6b**).* Elution with cyclohexane/ethyl acetate 85:15, after **5b**, gave **6b** as thick colourless oil; [Found: C, 53.4; H 4.0. $C_{30}H_{28}Br_2O_8$ requires C, 53.27; H, 4.17%]; ν_{max} (Nujol mull) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.37 (4H, d, *J* 8.4 Hz, *orto*-Br aromatic protons), 7.04 (4H, d, *J* 8.4 Hz, *meta*-Br aromatic protons), 6.79 (1H, s, H6),

6.35 (1H, s, H3), 4.82 (2H, t, *J* 7.6 Hz, benzylic proton), 3.84 (6H, s, 2 O*Me*), 3.76 (6H, s, 2 O*Me*), 3.54 (2H, dd, *J* 17.1, 7.7 Hz, 2C*H*H), 3.47 (2H, dd, *J* 17.1, 7.7 Hz, 2CH*H*); δ_C (75 MHz $CDCl_3$) 191.7, 165.3, 160.7, 156.0, 151.2, 141.5, 130.9, 129.0, 127.2, 121.9, 119.6, 95.1, 55.0, 52.5, 43.4, 38.1.

*4.2.10. Methyl 4-(2,3,4-trimethoxyphenyl)-2-oxo-4-phenylbutanoate (**4ac**).* Eluant: cyclohexane/ethyl acetate 80:20, colourless oil; [Found: C, 67.2; H, 6.2. $C_{20}H_{22}O_6$ requires C, 67.03; H, 6.19%]; ν_{max} (liquid film) 1730 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.29–7.25 (4H, m, aromatic protons), 7.20 (1H, m, aromatic proton), 6.75 (1H, d, *J* 8.6 Hz, H6 aromatic proton), 6.63 (1H, d, *J* 8.6 Hz, H5 aromatic proton), 4.94 (1H, t, *J* 7.7 Hz, benzylic proton), 3.84 (9H, s, 3 O*Me*), 3.70 (3H, s, O*Me*), 3.59 (2H, d, *J* 7.7 Hz, CH_2); δ_C (75 MHz $CDCl_3$) 191.8, 160.8, 152.1, 151.0, 142.9, 141.9, 128.7, 127.9, 127.3 125.9, 121.4, 106.5, 60.1, 55.4, 52.4, 44.2, 38.6.

*4.2.11. Methyl 4-(4-bromophenyl)-4-(2,3,4-trimethoxyphenyl)-2-oxobutanoate (**4bc**).* Eluant: cyclohexane/ethyl acetate 85:15, colourless oil; [Found: C, 55.1; H 5.0. $C_{20}H_{21}BrO_6$ requires C, 54.93; H 4.84%]; ν_{max} (liquid film) 1732 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.40 (2H, d, *J* 8.4 Hz, *ortho*-Br aromatic protons), 7.14 (2H, d, *J* 8.4 Hz, *meta*-Br aromatic protons), 6.85 (1H, d, *J* 8.6 Hz, H6 aromatic proton), 6.62 (1H, d, *J* 8.6 Hz, H5 aromatic proton), 4.88 (1H, t, *J* 7.6 Hz, benzylic proton), 3.84 (9H, s, 3 O*Me*), 3.71 (3H, s, O*Me*), 3.56 (2H, d, *J* 7.6 Hz, CH_2); δ_C (75 MHz $CDCl_3$) 191.5, 160.7, 152.3, 151.0, 142.0, 141.95, 131.0, 129.1, 128.0, 121.2, 119.7, 106.5, 60.1, 55.4, 52.5, 43.9, 38.1.

*4.2.12. Methyl 4-(4-dimethylamino-2-methoxyphenyl)-2-oxo-4-phenylbutanoate (**4ad**).* Eluant: cyclohexane/ethyl acetate 85:15, **4ad** was eluted first as a colourless oil; [Found: C, 70.5; H, 6.7; N, 4.2. $C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N 4.10%]; ν_{max} (liquid film) 1730 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.30 (4H, m, aromatic protons), 7.20 (1H, m, aromatic proton), 6.94 (1H, d, *J* 8.3 Hz, H6 aromatic proton), 6.28 (2H, m, H3 and H5 aromatic proton), 4.95 (1H, t, *J* 7.7 Hz, benzylic proton), 3.84 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.65 (1H, dd, *J* 17.2, 7.7 Hz, 2C*H*H), 3.49 (1H, dd, *J* 17.2, 7.6 Hz, 2CH*H*), 2.95 (6H, s, NMe_2); δ_C (75 MHz $CDCl_3$) 192.2, 160.9, 157.0, 150.3, 143.1, 128.1, 127.8, 127.4, 119.3, 104.3, 95.9, 54.7, 52.3, 44.2, 40.2, 38.2.

*4.2.13. Dimethyl 3-[(4-dimethylamino-2-methoxyphenyl)(phenyl) methyl]-2,6-dioxo-4-phenylheptandioate (**7**).* The elution with cyclohexane/ethyl acetate 85:15, after **4ad**, gave **7** as thick light yellow oil; [Found: C, 69.9; H, 6.2; N, 2.4. $C_{31}H_{33}NO_7$ requires C, 70.04; H, 6.26; N, 2.63%]; ν_{max} (Nujol mull) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.34 (1H, d, *J* 8.4 Hz, H6 aromatic proton), 7.28–6.99 (m, 10H, aromatic protons), 6.37 (1H, dd, *J* 8.4, 1.8 Hz, H5 aromatic proton), 6.10 (1H, d, *J* 1.8 Hz, H3 aromatic proton), 4.99 (1H, dd, *J* 11.7, 6.7 Hz, H3), 4.63 (1H, d, *J* 11.7 Hz, H benzyl), 3.80 (1H, m, H4), 3.83 (3H, s, O*Me*), 3.77 (3H, s, O*Me*), 3.46 (3H, s, O*Me*), 3.26 (1H, dd, *J* 18.4, 6.7 Hz, H5), 3.10 (1H, dd, *J* 18.4, *J* 7.6 Hz, 1H, H5′), 2.95 (6H, s, NMe_2); δ_C (75 MHz $CDCl_3$) 195.6, 191.0, 161.4, 160.3, 157.0, 150.4, 142.2, 139.0, 128.5, 127.9, 127.8, 127.5, 126.5, 125.6, 117.4, 104.6, 95.8, 54.6, 52.2, 43.9, 42.6, 40.7, 40,1.

*4.2.14. Dimethyl 3-[(4-dimethylamino-2-methoxyphenyl)(phenyl) methyl]-2,6-dioxo-4-phenylheptanedioate (**8**).* The elution with cyclohexane/ethyl acetate 85:15, after **7**, gave **8** as thick oil; [Found: C, 70.0; H, 6.2; N, 2.7. $C_{31}H_{33}NO_7$ requires C, 70.04; H, 6.26; N, 2.63%]; ν_{max} (Nujol mull) 1733 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.47 (1H, d, *J* 8.4 Hz, H6 aromatic proton), 7.32–7.07 (10H, m, aromatic protons), 6.17 (1H, dd, *J* 8.4, 2.2 Hz, H5 aromatic proton), 6.07 (1H, d, *J* 2.2 Hz, H3 aromatic proton), 4.94 (1H, dd, *J* 11.3, 7.4 Hz, H3), 4.66 (1H, d, *J* 11.3 Hz, H benzyl), 3.81 (1H, m, H4), 3.76 (3H, s, O*Me*), 3.75 (3H, s, O*Me*), 3.54 (3H, s, O*Me*), 3.06 (1H, d, *J* 7.25 Hz, H5), 2.94 (1H, d, *J* 6.7 Hz, H5′), 2.86 (6H, s, NMe_2); δ_C (75 MHz $CDCl_3$) 194.5, 191.2, 161.1, 160.2, 156.6, 150.2, 142.1, 139.4, 128.5, 128.12, 128.06, 127.7, 127.5, 126.6, 125.9, 118.0, 104.4, 95.9, 54.7, 52.8, 52.3, 52.1, 44.6, 43.3, 41.5, 40,0.

*4.2.15. Methyl 4-(4-bromophenyl)-4-(4-dimethylamino-2-methoxy phenyl)-2-oxolbutanoate (**4bd**).* Eluant: cyclohexane/ethyl acetate 80:20, light yellow crystals, mp 104–105 °C (cyclohexane/hexane); [Found: C, 57.2; H, 5.3; N, 3.2. $C_{20}H_{22}BrNO_4$ requires C, 57.15; H, 5.28; N 3.33%]; ν_{max} (Nujol mull) 1732 cm^{-1} (C=O); δ_H (300 MHz $CDCl_3$) 7.39 (2H, d, *J* 8.4 Hz, *ortho*-Br aromatic protons), 7.16 (2H, d, *J* 8.4 Hz, *meta*-Br aromatic protons), 6.92 (1H, d, *J* 8.4 Hz, H6 aromatic proton), 6.27 (1H, dd, *J* 8.4, 2.4 Hz, H5 aromatic proton), 6.22 (1H, d, *J* 2.4 Hz, H3 aromatic proton), 4.87 (1H, t, *J* 7.6 Hz, benzylic proton), 3.84 (3H, s, O*Me*), 3.78 (3H, s, OCH_3), 3.61 (1H, dd, *J* 17.0, 8.0 Hz, C*H*H), 3.47 (1H, dd, *J* 17.0, 7.25 Hz, 2CH*H*), 2.94 (6H, s, NMe_2); δ_C (75 MHz $CDCl_3$) 191.9, 160.8, 156.9, 150.4, 142.3, 130.8, 129.2, 127.9, 119.4, 118.5, 104.1, 95.7, 54.6, 52.4, 43.9, 40.1, 37.8.

4.3. Reaction between methyl 4-(4-bromophenyl)-4-(2,4-dimethoxyphenyl)-2-oxobutanoate (4bb) and (*E*)-2-oxo-4-(4-bromophenyl)-but-3-enoic acid methyl ester (1b)

In a rubber septum sealed vial a mixture of **4bb** (0.022 g, 0.055 mmol), scandium triflate (0.010 g, 0.02 mmol) and **1b** (0.018 g, 0.067 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was stirred for 8 h at ambient temperature. The reaction was decomposed in water, extracted with CH_2Cl_2, dried, and the reaction mixture was column chromatographed (silicagel, 30 cm length, 1.5 cm diameter) with cyclohexane/ethyl acetate 85:15 as eluant. The fractions of unreacted **1b** (0.007 g) and **4bb** (0.009 g) were eluted first, then one diastereomeric methyl 4-[5-(3-methoxycarbonyl-3-oxo-1-(4-bromophenyl)propyl)-2,4-dimethoxyphenyl]-2-oxo-4-(4-bromo phenyl)butanoate (**5b**, 0.0035 g—10% yield) was separated, followed by its stereoisomer **6b** (0.0175 g—49% yield). The ^1H NMR and IR spectra of **5b** and **6b** were identical to those previously described.

4.4. Reaction catalyzed by [scandium triflate/pybox (3)] complex. General procedure

E)-2-Oxo-4-arylbut-3-enoic acid methyl ester (**1a–c**) (0.33 mmol), pybox 3 (0.03 mmol), scandium triflate (0.03 mmol) and molecular sieves 3 Å (about 0.040 g) were added to anhydrous CH_2Cl_2 (0.3 mL) at ambient temperature in a rubber septum sealed vial. The mixture was stirred for 15 min and then cooled at the temperature reported in Table 1–3. The required arene (**2a–d**) (0.40 mmol) was added (when liquid with a microsyringe) and stirring was continued for the time reported in Tables 1–3. The reaction was decomposed in water, extracted with CH_2Cl_2, dried, and the reaction mixture was separated by column chromatography (silicagel, 30 cm length, 1.5 cm diameter) with the eluant reported above for each single product. The enantiomeric mixtures were HPLC analyzed under the conditions reported below for each product, and the [α] value was determined.

*4.4.1. (+)-Methyl 4-(2,4,6-trimethoxyphenyl)-2-oxo-4-phenylbu-tanoate (**4aa**).* The mixture of enantiomers was analyzed on a Chiralpak AD column with hexane/2-propanol [96:4] as eluant (1.0 mL/min) and the average retention times were: 16 (minor enantiomer) and 19.7 min (major enantiomer). ee 99.5%. $[\alpha]_D^{20}$ +44.5 (*c* 5.3, $CHCl_3$).

*4.4.2. (+)-Methyl 4-(4-bromophenyl)-4-(2,4,6-trimethoxyphenyl)-2-oxobutanoate (**4ba**).* The mixture of enantiomers was analyzed on a Chiralpak AD column with hexane/2-propanol [96:4] as eluant (1.0 mL/min) and the average retention times were: 15.8 (minor

enantiomer) and 24.4 min (major enantiomer). ee 99%. $[\alpha]_D^{20}$ +29.2 (*c* 0.5, $CHCl_3$).

*4.4.3. (+)-Methyl 4-(2,4,6-trimethoxyphenyl)-4-(4-nitrophenyl)-2-oxobutanoate (**4ca**).* The mixture of enantiomers was analyzed on a Chiralpak AD column with hexane/2-propanol [90:10] as eluant (1.0 mL/min) and the average retention times were: 19.7 (minor enantiomer) and 27.8 min (major enantiomer). ee 95.5%. $[\alpha]_D^{20}$ +90.9 (*c* 3.4, $CHCl_3$).

*4.4.4. (+)-(4R)-Methyl 4-(2,4-dimethoxyphenyl)-2-oxo-4-phenyl butanoate (**4ab**).* The mixture of enantiomers was analyzed on a Chiralpak AD column with hexane/2-propanol [95:5] as eluant (1.0 mL/min) and the average retention times were: 16.6 (minor enantiomer) and 18.7 (major enantiomer) [lit.[2] Chiralpak AD column, hexane/2-propanol [95:5], (0.5 mL/min), retention times: 23.8 (minor enantiomer) and 26.6 min (major enantiomer)]. ee 93%. $[\alpha]_D^{20}$ +24.6 (*c* 1.6, $CHCl_3$); $[\alpha]_D^{20}$ +25.4 (*c* 1.5, CH_2Cl_2) [lit.[2]: $[\alpha]_D^{20}$ +15.0 (*c* 1.02, CH_2Cl_2) for 60% ee].

*4.4.5. (+)-Methyl 4-(4-bromophenyl)-4-(2,4-dimethoxyphenyl)-2-oxobutanoate (**4bb**).* The mixture of enantiomers was analyzed on a Chiralpak AD column with hexane/2-propanol [90:10] as eluant (1.0 mL/min) and the average retention times were: 14.4 (minor enantiomer) and 16.7 min (major enantiomer). ee 80%. $[\alpha]_D^{20}$ +44.5 (*c* 5.3, $CHCl_3$).

*4.4.6. (+)-Methyl 4-(4-dimethylamino-2-methoxyphenyl)-2-oxo-4-phenylbutanoate (**4ad**).* The mixture of enantiomers was analyzed on a Chiralpak AD column with hexane/2-propanol [96:4] as eluant (1.0 mL/min) and the average retention times were: 21.5 (minor enantiomer) and 24.4 min (major enantiomer). ee 92%. $[\alpha]_D^{20}$ +35.2 (*c* 0.7, $CHCl_3$).

*4.4.7. (+)-Methyl 4-(4-bromophenyl)-4-(4-dimethylamino-2-methoxyphenyl)-2-oxobutanoate (**4bd**).* The mixture of enantiomers was analyzed on a Chiralpak AD column with hexane/2-propanol [96:4] as eluant (1.0 mL/min) and the average retention times were: 24.6 (minor enantiomer) and 31 min (major enantiomer). ee 92%. $[\alpha]_D^{20}$ +36.8 (*c* 3.6, $CHCl_3$).

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca (MUR) and by the University of Pavia.

Supplementary data

The ^1H- and ^{13}C NMR spectra of **4** obtained from Sc^{III}-catalyzed Friedel–Crafts and some significant HPLC chromatograms of optically active products obtained from [pybox **3**/Sc^{III}]-catalyzed reactions are reported. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.02.054.

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