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TETRAHEDRON

A Novel Method for the Efficient Synthesis of Methyl 2-Oxo-2-arylacetates and Its Application to the Preparation of Fungicidal Methyl (*E*)-*O*-Methyloximino-2-arylacetates and Their (*Z*)-Stereoisomers

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This paper is dedicated to the memory of the late Professor Giacomino Randazzo

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Abstract : Methyl 2-oxo-2-arylacetates **1**, which include some fluorinated compounds, have been synthesized in moderate to excellent yields by reaction of methyl oxalyl chloride with arylzinc halides in the presence of $Pd(PPh_3)_4$. The highest yields have been obtained when these reactions involved arylzinc bromides which were prepared by conversion of the corresponding aryl bromides to organolithiums, followed by transmetallation with $ZnBr_2$. Compounds **1** have been converted in high yields to the corresponding (*E*)- and (*Z*)-*O*-methyloximino-2-arylacetates (*E*)- and (*Z*)-**5** by treatment with *O*-methylhydroxylamine hydrochloride in pyridine. Compounds (*E*)- and (*Z*)-**5** have been easily separated by MPLC on silica gel and their structure and stereochemistry have been assigned by NMR techniques. So prepared compounds of general formula **5** included an agrochemically important fungicide, *i.e.* (*E*)-**5c**, its fluorinated structural analogues, as well as compounds which proved to be able to delay the growth of fungal species isolated from deteriorated papers. Interestingly, several compounds of general formula (*Z*)-**5** underwent partial stereomutation in the presence of daylight and catalytic amounts of iodine.

The methods used for the synthesis of α-ketoesters of general formula **1** include Friedel-Crafts acylation,[1] hydrolysis and esterification of acyl cyanides,[2] oxidative cleavage of cyano keto phosphoranes,[3] the reaction between organolithium reagents and triethoxyacetonitrile followed by hydrolysis,[4] the Pd-catalyzed double carbonylation of aryl halides[5] and the $ZnCl_2$-promoted addition of 1,2-diethoxy-1,2-disilyloxyethylene to electrophiles such as carbonyl compounds or *tert*-alkyl halides.[6] Nevertheless, the method which involves the coupling reaction between organometallic species of general formula **2** and oxalic ester derivatives **3** appears to be one of the most simple and versatile strategies for the preparation of compounds **1** (Scheme 1). Several procedures for the synthesis of compounds **1** according to this strategy have been reported in the literature.[7-14] As shown in Scheme 1, the organometallic species **2** which have been used in these procedures include Grignard reagents,[7,8,11,12] organolithiums,[9,11] organocopper/zinc reagents,[10] organocopper compounds derived from Grignard reagents, copper(I) bromide and lithium bromide[13] as well as organostannanes.[14] On the other hand, the oxalic ester derivatives **3**, which have been employed as electrophilic partners in these reactions, include alkyl α-oxo-1*H*-imidazole-1-acetates **3a**,[7] 1-(N-alkoxyoxalyl-N-methylamino)-3-methylimidazolium salts **3b**,[8] the monoethyl oxalic acid N-methoxy-N-methylamide **3c**,[9] alkyl oxalyl chlorides **3d**,[10,13,14] diethyl oxalate **3e**[11] as well as ethyl (2,6-di-*tert*-butyl-4-methoxyphenyl)oxalate **3e** (R^1 = 2,6-di-*tert*-butyl-4-methoxyphenyl).[12] Unfortunately, most of these coupling reactions are not free from side reactions,[9,11c,13] require the

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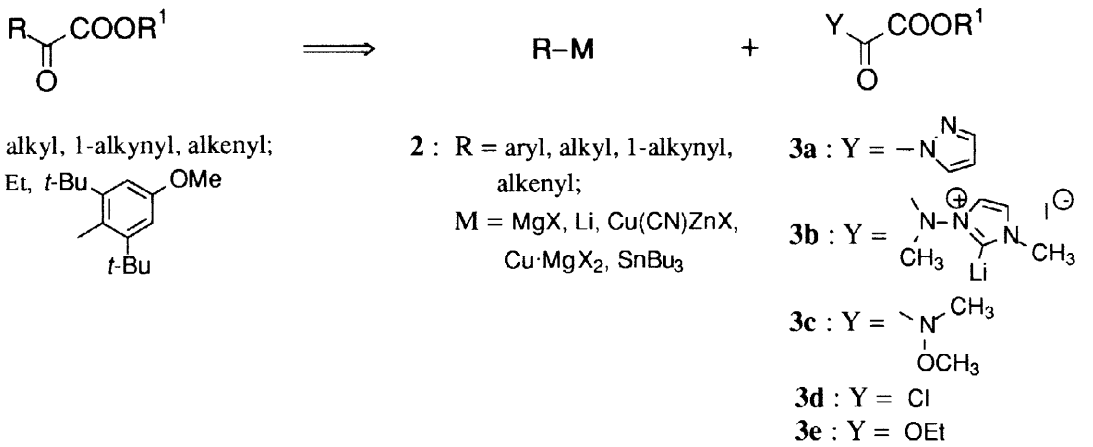
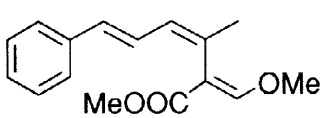
use of not commercially available oxalic ester derivatives[7-9] and/or afford the desired α-ketoesters **1** in modest yields.[7,11b,11c,14]

Scheme 1



In connection with ongoing projects on the synthesis of photostable analogues of strobilurin A **4**, which are able to control fungi which affect crops and/or to inhibit the growth of fungal species which deteriorate papery materials,[15,16] we recently directed our attention to developing a new, selective and efficient method for the synthesis of methyl 2-oxo-2-arylacetates of general formula **1**. This was based on the strategy illustrated in Scheme 1 and in which a commercially available oxalic ester derivative was used. In fact, we speculated that compounds **1** might be suitable starting materials for the synthesis of strobilurin A analogues of general formula (*E*)-**5** possessing potential fungicidal activity, which are structurally related to *Kresoxime methyl* **6**, an agrochemical fungicide developed by BASF,[17a,b] and, similarly to this substance, are characterized by direct attachment of the methyl (*E*)-*O*-methyloximinoacetate group **7** to a substituted aromatic ring. It must be noted that this group and the methyl (*E*)-β-methoxypropenoate toxophore **8**, which characterizes either naturally-occurring **4** or its synthetic fungicidal mimics in which this toxophore is linked to a substituted (hetero)aromatic ring,[15-18] are isosteric. Moreover, it should be mentioned that, although the patent literature documents that several compounds of general formula (*E*)-**5** exhibit high fungicidal activity,[17] some methyl *O*-methyloximino-2-aryl acetates **5** having undefined[19] or (*Z*)-stereochemistry[20] have also been found to be able to control agrochemically important fungi.



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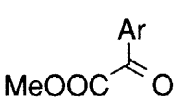

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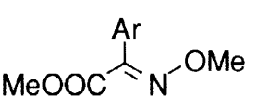
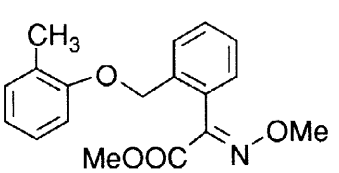


(*E*)-**5**



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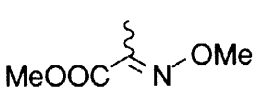

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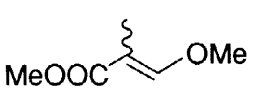

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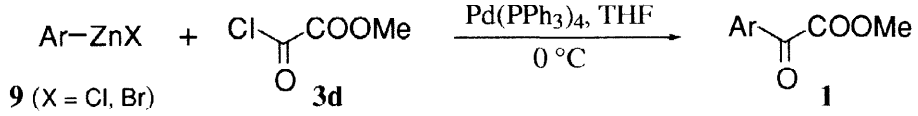
We now wish to report that compounds **1**, some of which are characterized by a trifluoromethyl substituted aromatic moiety, can be smoothly, efficiently and selectivey synthesized by Pd-catalyzed cross-coupling reaction between arylzinc halides **9** and methyl oxalyl chloride **3d**. Moreover, we wish to describe that: *i)* compounds **1** can be converted in high yield into stereoisomeric mixtures of the corresponding methyl (*E*)- and (*Z*)-*O*-methyloximino-2-arylacetates (*E*)- and (*Z*)-**5**; *ii)* compounds (*E*)-and (*Z*)-**5**, which possess potential fungicidal activity, can be easily separated by MPLC on silica gel; *iii)* some compounds of general formula (*Z*)-**5** undergo partial stereomutation in the presence of daylight and catalytic amounts of iodine.

Finally, we will summarize preliminary data which show that some compounds of general formula (*E*)- and (*Z*)-**5** so prepared are able to delay the growth of fungal species isolated from deteriorated papers.

RESULTS AND DISCUSSION

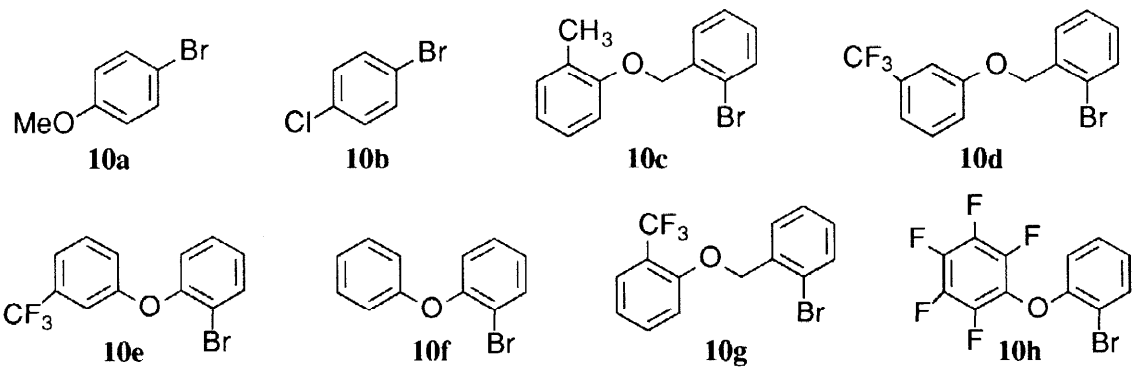
Synthesis of methyl 2-oxo-2-arylacetates

As above mentioned, our initial goal was the development of a new efficient method for the synthesis of methyl 2-oxo-2-arylacetates **1** in which a cheap commercially available oxalic ester derivative was used as starting material. After a great deal of experimentation we found that compounds **1** could be prepared in moderate to excellent yields by reaction of 1.2 equiv of arylzinc halides **9** (X = Cl, Br) with methyl oxalyl chloride **3d** in THF at 0 °C, in the presence of catalytic amounts of $Pd(PPh_3)_4$ (eq. 1).



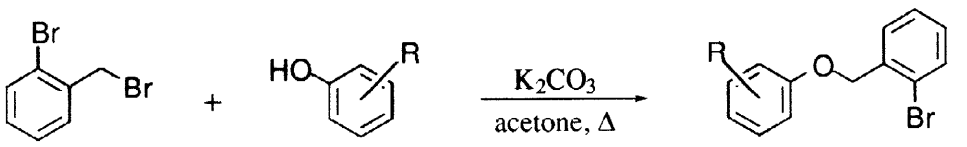
(1)

Among the aryl bromides of general formula **10**, which we used or we attempted to use as starting materials for the preparation of the arylzinc halides **9**, compounds **10a** and **10b** were commercially available and **10f** was prepared according to the literature.[21]



Compounds **10c**, **10d** and **10g** were synthesized in 93, 96 and 97 % yield, respectively, by reaction of 2-

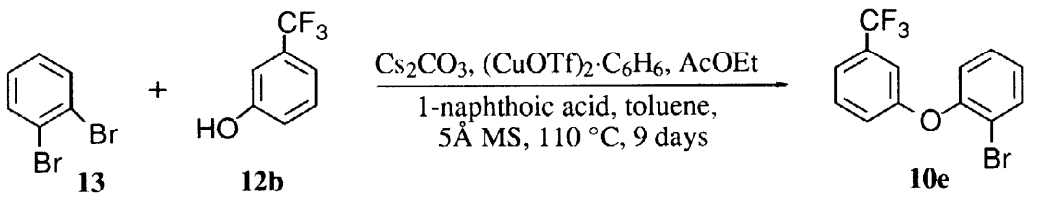
bromobenzyl bromide **11** with 1 equiv of *o*-cresol **12a**, α,α,α-trifluoro-*m*-cresol **12b** and α,α,α–trifluoro-*o*-cresol **12c**, respectively, in refluxing acetone, in the presence of 1 equiv of anhydrous K_2CO_3 (eq. 2).



(2)

11 **12a** : R = 2-CH_3 **10c** : R = 2-CH_3
12b : R = 3-CF_3 **10d** : R = 3-CF_3
12c : R = 2-CF_3 **10g** : R = 2-CF_3

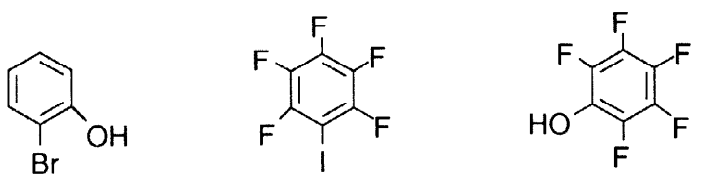
On the other hand, compound **10e** was prepared starting from *o*-dibromobenzene **13** and **12b** according to a recently general procedure for the synthesis of diaryl ethers.[22] In particular, compound **13** was reacted with 2 equiv of **12b** in toluene at 110 °C for 9 days, in the presence of molecular sieves 5Å, 2 equiv of Cs_2CO_3, 5 mol % $(CuOTf)_2{\cdot}C_6H_6$, 5 mol % ethyl acetate and 1.4 equiv of 1-naphthoic acid, to give the desired (aryloxy)aryl bromide **10e** in 53 % yield (eq. 3).



(3)

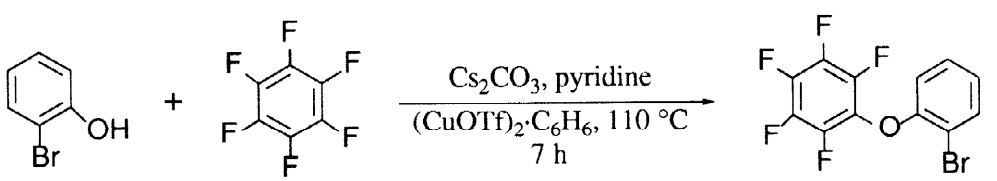
13 **12b** **10e**

Unfortunately, this protocol proved to be unsuitable for the synthesis of **10h** starting from *o*-bromophenol **14** and iodopentafluorobenzene **15**.



14 **15** **16**

Moreover, an attempt to prepare **10h** by reaction between the sodium salt derived from pentafluorophenol **16** and 1.3 equiv of **13** in pyridine at 110 °C, in the presence of 15 mol % CuBr, was also unsuccessful. However, it was eventually found that treatment of *o*-bromophenol **14** with 2.6 equiv of hexafluorobenzene **17** and 1 equiv of Cs_2CO_3 in pyridine at 110 °C for 7 h in the presence of 2.5 mol % $(CuOTf)_2{\cdot}C_6H_6$, gave 96 % chemically pure **10h** in 63 % yield (eq. 4).



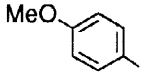
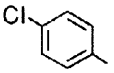
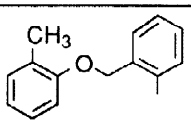
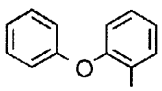
(4)

14 **18** **10h**

Among the aryl bromides of general formula **10**, compounds **10a-g** were converted into the

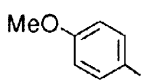
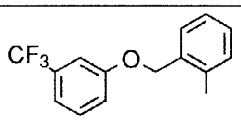
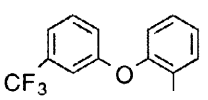
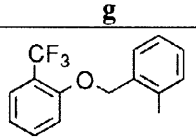
corresponding organozinc halides **9a-g** (X = Cl, Br) according to two different protocols. The first of these (*Procedure A*), which was used to prepare compounds **9a-c** (X = Cl) and **9f** (X = Cl), involved the conversion of **10a-c** and **10f** to the corresponding organomagnesium bromides followed by transmetallation with a slurry of dry $ZnCl_2$ (1.3 equiv) in THF at 0 °C (eq. 5).

$$\text{Ar–Br}\ (\mathbf{10a\text{-}c, 10f}) \xrightarrow[2)\ ZnCl_2,\ THF,\ 0\ ^\circ C]{1)\ Mg,\ THF,\ \Delta} \text{Ar–ZnCl}\ (\mathbf{9a\text{-}c, 9f}) \qquad (5)$$

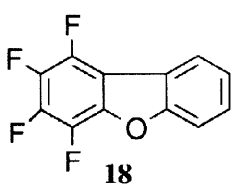
	a	b	c	f
Ar				

Unfortunately, this protocol proved to be unsuitable to prepare **9d** (X = Cl) from **10d**. In fact, an attempt to prepare a THF solution of the Grignard reagent derived from **10d** gave an unsatisfactory result, this Grignard reagent being obtained in low yield. On the other hand, compounds **9d,e** (X = Br), **9g** (X = Br) as well as **9a** (X = Br) were successfully prepared from the corresponding aryl bromides, *i.e.* **10d**, **10e**, **10g** and **10a**, respectively, using the general procedure reported in the literature for the synthesis of functionalized organozinc halides via the corresponding organolithiums.[23] (*Procedure B*). In particular, the above mentioned aryl bromides were converted into the corresponding organolithiums by the slow addition of a solution of butyllithium (1.05 equiv) in hexane to the aryl bromides dissolved in a THF/Et_2O/hexane mixture (4: 1: 1) which was maintained at - 100 °C. After 12-25 min a solution of dry $ZnBr_2$ (1.25 equiv) in THF was added at - 100 °C affording stable solutions of the desired arylzinc bromides (eq. 6).

$$\text{Ar–Br}\ (\mathbf{10a, 10d\text{-}e, 10g}) \xrightarrow[2)\ ZnBr_2,\ THF,\ -100\ \text{to}\ 20\ ^\circ C]{1)\ BuLi,\ THF,\ Et_2O,\ \text{hexane},\ -100\ ^\circ C} \text{Ar–ZnBr}\ (\mathbf{9a, 9d\text{-}e, 9g}) \qquad (6)$$

	a	d	e	g
Ar				

However, an attempt to efficiently prepare 2-(pentafluorophenoxy)phenylzinc bromide **9h** starting from **10h** acccording to this protocol was unsuccessful. In fact, it was observed that hydrolysis of the reaction mixture, which was obtained by addition of butyllithium (1.05 equiv) to a solution of **10h** in a THF/Et_2O/hexane mixture (4 :1: 1) at - 100 °C followed by treatment at - 100 °C with a THF solution of dry $ZnBr_2$ (1.25 equiv), produced a mixture of two components in a 26 : 74 molar ratio. The major component had a MS spectrum which was consistent with that corresponding to compound **18** and the minor component corresponded to compound **19**, which derived from hydrolysis of **9h**.



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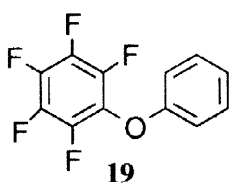

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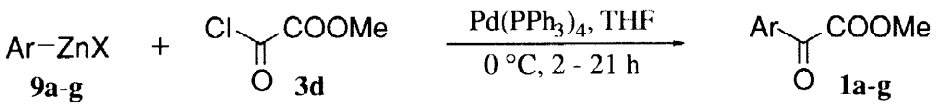
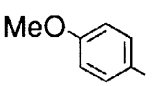
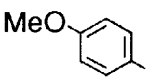
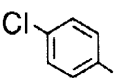
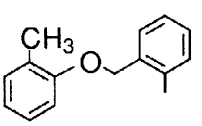
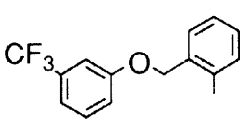
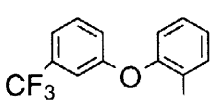
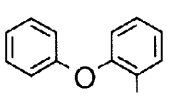
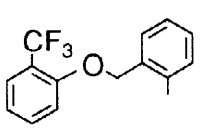
On the basis of this result, no attempt was made to use so prepared **9h** for the synthesis of the corresponding methyl 2-oxo-2-arylacetate. Table 1 summarizes the results of the Pd-catalyzed reactions between **3d** and the organozinc halides **9a-g**. Data inspection reveals that the desired compounds **1** were obtained in high yields (84-91 %) when the reactions were performed using arylzinc bromides prepared according to *Procedure B* (entries 2, 5, 6 and 8, Table 1). It should also be noted that these reactions were very clean and proceeded in a short time at 0 °C. On the contrary, lower but still satisfactory yields were obtained when the reactions involved arylzinc chlorides which were prepared according to *Procedure A* (entries 1, 3, 4 and 7, Table 1).

Table 1. Synthesis of methyl 2-oxo-2-arylacetates **1a-g** by Pd-catalyzed reaction between organozinc halides **7a-g** and methyl oxalyl chloride **3d**.[a)]



Entry	Organozinc halide			Reaction time (h)	Product	Isolated yield (%) [b)]
	9	Ar	X		**1**	
1	**9a** [c)]		Cl	14.0 [d)]	**1a**	52
2	**9a** [e)]		Br	3.5	**1a**	91
3	**9b** [c)]		Cl	4.5	**1b**	60
4	**9c** [c)]		Cl	4.0	**1c**	61
5	**9d** [e)]		Br	3.5	**1d**	91
6	**9e** [e)]		Br	5.5	**1e**	84
7	**9f** [c)]		Cl	21.0	**1f**	74
8	**9g** [e)]		Br	6.0	**1g**	91

a) Unless otherwise reported the reactions between **3d** and compounds **9** (1.2 equiv) were carried out at 0 °C in the presence of 5 mol % $Pd(PPh_3)_4$. b) Based on methyl oxalyl chloride **3d**. c) This organozinc chloride was prepared according to *Procedure A*. d) This reaction was carried out for 14 h at -20 °C and for 16 h at 0 °C. e) This organozinc bromide was prepared according to *Procedure B*.

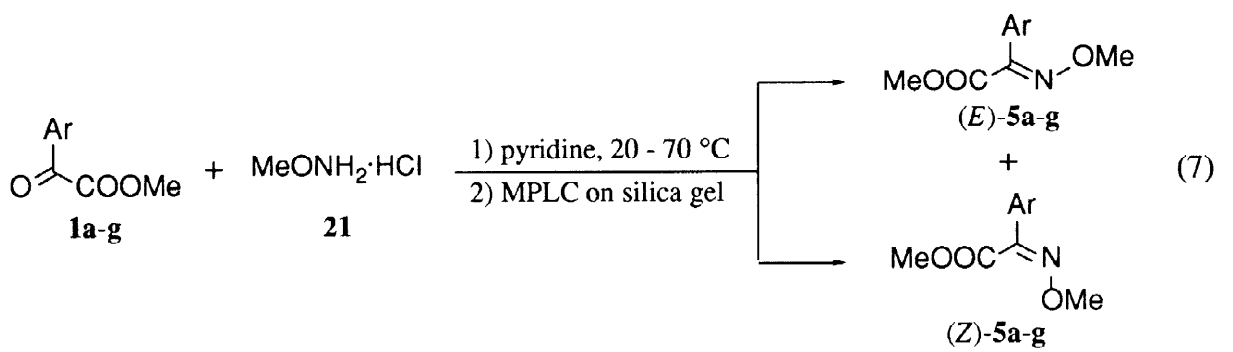
Moreover, the crude products, which were obtained from these reactions, proved to be contaminated by small amounts of byproducts which included homo-coupled products derived from arylzinc chlorides as well as decarbonylated cross-coupled compounds.

Very likely, the fact that the Pd-catalyzed reactions involving arylzinc chlorides afforded yields, which were lower than those which were obtained when arylzinc bromides were used, was mainly to be ascribed to the lower reactivity of arylzinc chlorides in the step of the catalytic cycle which corresponds to the transmetallation reaction. On the other hand, the possibility that these lower yields were essentially due to the presence of magnesium halides in the THF solutions of the arylzinc chlorides prepared according to *Procedure A* via the corresponding Grignard reagents could be excluded. In fact, it was found that when a THF slurry of $MgBr_2$, which was obtained by reaction of 1,2-dibromoethane and Mg in THF, was added to an equimolar amount of **9d** (X = Br) prepared according to *Procedure B* and the resulting mixture was used in a Pd-catalyzed reaction with **3d** under the same conditions used in entry 5 of Table 1, the desired cross-coupled product **1d** was obtained in a yield (83 %) which was comparable to that obtained (91 %) when **1d** was synthesized from **9d** free of $MgBr_2$ (entry 5, Table 1).

Finally, it must also be mentioned that pre-catalysts different from $Pd(PPh_3)_4$ were also tested in the Pd-catalyzed reaction between **9b** (X = Cl) and **3d**. However, it was found that those constituted of $Pd(dba)_2$ and $AsPh_3$ (Pd : As = 1 : 1), $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (Pd : dppf = 1 : 1) were less efficient than $Pd(PPh_3)_4$ and afforded the desired cross-coupled product, **1b**, contaminated by significant amounts of byproducts.

Methyl (*E*)- and (*Z*)-*O*-methyloximino-2-arylacetates

With an efficient route to compounds **1a-g** established, we next investigated the use of these α-ketoesters for the preparation of the corresponding methyl (*E*)-*O*-methyloximino-2-arylacetates (*E*)-**5a-g** and their (*Z*)-stereoisomers. We found that treatment of **1a-g** with an excess (2.8 - 4 equiv) of *O*-methylhydroxylamine hydrochloride **20** in pyridine at 20 - 70 °C provided cleanly stereoisomeric mixtures of compounds (*E*)- and (*Z*)-**5a-g** in high yield.

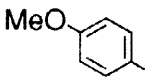
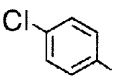
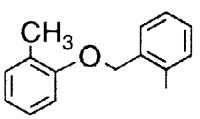
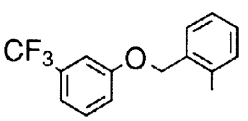
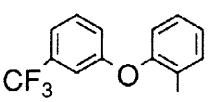
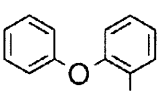
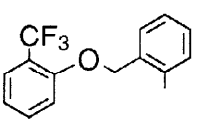


(7)

Interestingly, these stereoisomers could be easily separated in pure form by MPLC on silica gel (eq. 7). As shown in Table 2, where the results obtained in the preparation of compounds (*E*)- and (*Z*)-**5a-g** are summarized, all reactions provided stereoisomeric mixtures, but compounds (*E*)-**5c**, (*E*)-**5d**, and (*E*)-**5g** were the major components of the stereoisomeric mixtures which were obtained by reaction of the corresponding α-ketoesters with **20** (entries 3, 4 and 7, Table 2). On the contrary, (*E*)-**5b** (entry 2, Table 2), (*E*)-**5e** (entry 5,

Table 2), (*E*)-**5 f** (entry 6, Table 2) as well as (*E*)-**5 a**, which was obtained from a reaction performed at 70 °C (entry 1, Table 2), were the minor components of the corresponding stereoisomeric mixtures. It is also interesting to note that methyl *O*-methyloximino-2-arylacetates so prepared included compound (*E*)-**5 c**, which is known to be an agrochemically important and commercially available fungicide, its (*Z*)-stereoisomer as well as the trifluoromethyl analogues of these substances, *i.e.* compounds (*E*)- and (*Z*)-**5g**, respectively.

Table 2. Synthesis of methyl (*E*)- and (*Z*)-*O*-methyloximino-2-arylacetates, (*E*)- and (*Z*)-**5**, from compounds **1** and *O*-methylhydroxylamine hydrochloride **20**.

Entry	Reagent		**20 / 1** Molar ratio	Reaction conditions (T / h)	Product			
	1	Ar			**5**	(*E*) / (*Z*)-**5** molar ratio (*)	Isolated yield(%)	
							(*E*)-**5**	(*Z*)-**5**
1	**1a**		4.0	70 / 17.5	**5a**	17: 83	12	56
2	**1b**		2.8	20 / 17.5	**5b**	28: 72	24	63
3	**1c**		3.0	20 / 17.5	**5c**	69: 31	63	28
4	**1d**		3.0	20 / 17.5	**5d**	75: 25	71	25
5	**1e**		3.0	20 / 17.5	**5e**	44: 56	46	52
6	**1f**		3.0	20 / 17.5	**5f**	45: 55	41	53
7	**1g**		3.0	20 / 6, then 37 / 6	**5g**	57: 43	56	42

(*) Evaluated by GLC of the crude reaction product.

We observed that all compounds of general formula **5**, to which the (*Z*)-configuration was assigned, had R_f values in their TLC analyses which were higher than those of the corresponding (*E*)-stereoisomers and that compounds (*Z*)-**5** were also first eluted by MPLC on silica gel. Moreover, GLC analyses, which were performed on a SE-30 bonded FSOT column or on an AT-35 bonded FSOT column, showed that all compounds of general formula (*E*)-**5** except (*E*)-**5 a** and (*E*)-**5b** had retention times lower than those of the corresponding (*Z*)-stereoisomers.

Compounds (*E*)- and (*Z*)-**5 a-g** were characterized by MS, IR, ^1H and ^{13}C NMR analyses as well as by

elemental analysis. Moreover, the structure and stereochemistry of all these compounds except (*E*)- and (*Z*)-**5b** were unambiguously assigned on the basis of their ^{1}H and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of NMR techniques which included 1D- or 2D-Overhauser experiments (NOESY), ^{1}H-^{13}C heteronuclear multi-quantum coherence (HMQC) experiments as well as ^{1}H-^{13}C long-range heteronuclear shift correlation. Interestingly, in compounds (*E*)-**5a** and (*E*)-**5c-g** the ^{13}C NMR signal assigned to the *O*-methyloximino group had a chemical shift value (δ 63.6 - 63.9 ppm) which was higher than that of the corresponding (*Z*)-stereoisomers (δ 62.8 - 63.3 ppm). On the contrary, the ^{13}C NMR signal assigned to the C=N group of (*E*)-**5a** and (*E*)-**5c-g** had a chemical shift value (δ 147.0 - 149.4 ppm) lower than that of the corresponding (*Z*)-stereoisomers (δ 147.2 - 150.7 ppm). Moreover, it was observed that in the ^{1}H NMR spectra of compounds (*E*)-**5a** and (*E*)-**5c-g** the signal assigned to the H-6 proton had a chemical shift value (δ 7.21 - 7.45 ppm) which was lower than that of this proton in the corresponding (*Z*)-stereoisomers (δ 7.35 - 7.83 ppm).

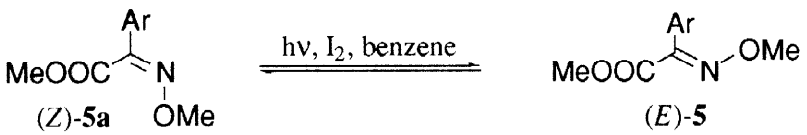
As regards the stereoisomers of **5b**, the following data allowed us to assign the (*E*)-stereochemistry to the minor component of the stereoisomeric mixture obtained from **1b** and **20** (entry 2, Table 2). Firstly, analogously to (*E*)-**5a** and (*E*)-**5c-g**, this minor component was last eluted in TLC and MPLC on silica gel. Secondly, some ^{13}C and ^{1}H NMR parameters of this minor component were found to be analogous to those of all other compounds (*E*)-**5**. In fact, the ^{13}C NMR signal assigned to the *O*-methyloximino group of this minor component had a chemical shift value (δ 63.7 ppm) which was higher than that of the corresponding stereoisomer (δ 63.0 ppm). Moreover, in the ^{13}C NMR spectrum of this minor component the signal assigned to its C=N group had a chemical shift value (δ 147.9 ppm) which was lower than that of this group (δ 149.3 ppm) in the major component of the stereoisomeric mixture. Finally, the ^{1}H NMR signal assigned to the H-6 proton of this minor component had a chemical shift value (δ 7.40 ppm) which was lower than that of this proton (δ 7.50 ppm) in the major component of the stereoisomeric mixture obtained from **20** and **1b**.

It must also be noted that when the ^{1}H and ^{13}C NMR spectra of (*Z*)-**5b** in $CDCl_3$ solution were registered it was observed that this compound underwent partial stereomutation. This observation prompted us to preliminarly investigate the stereochemical stability of compounds (*Z*)-**5a-g**. On the other hand, this investigation could allow us to establish if the stereoisomeric mixtures, which were obtained from **20** and compounds **1**, could be enriched in their (*E*)-stereoisomers. This possibility seemed quite interesting since, on the basis of the patent literature,[17] it could be expected that some compounds (*E*)-**5** among those synthesized had fungicidal activity higher than that of the corresponding (*Z*)-stereoisomers. Thus, 0.12 M benzene solutions of (*Z*)-**5a-g** and (*E*)-**5b** were treated with catalytic quantities of iodine at 20 - 63 °C in the presence of daylight and the corresponding reaction mixtures were periodically monitored by GLC (Table 3). As shown in this table, under the reaction conditions employed, compounds (*Z*)-**5a** and (*E*)-**5b** were found to be significantly stereochemically labile at 50 - 63 °C and 20 °C, respectively (entries 2 and 4, Table 3), and (*Z*)-**5c** and (*Z*)-**5f**, which were stereochemically stable at 20 °C, underwent stereomutation when their benzene solutions were heated for long periods of time (entries 6 and 10, Table 3). On the contrary, (*Z*)-**5d** proved to be stereochemically stable under these conditions (entry 7, Table 3) and (*Z*)-**5b**, (*Z*)-**5e** as well as (*Z*)-**5g** were found to be able to afford small amounts if their (*E*)-stereoisomers only after long periods of time at 20 °C or at 50 -63 °C (entries 3, 8 and 12, Table 3). However, all these data showed that no general conclusion on the relationship between structure and stereochemical stability of compounds (*Z*)-**5** could be drawn.

Finally, it is worth mentioning that in connection with our ongoing studies relating to the identification of compounds to be used for controlling the germination of the conidia and spores and the growth of fungal strains

isolated from deteriorated papers,[16,24] we undertook an investigation aimed at evaluating the bioactivity of some substances, among those of general formula (*E*)- and (*Z*)-**5** so prepared, against *Penicillium chrysogenum* and *Aspergillus parasiticus*.

Table 3. Stereomutation of compounds (*Z*)- and (*E*)-**5** in the presence of daylight and catalytic amounts of iodine [a].



(*Z*)-**5a** (*E*)-**5**

Entry	Reagent	Iodine (mol %)	Reaction conditions (days / °C)	Product	
				Compound	(*E*) / (*Z*)- ratio
1	(*Z*)-**5a**	5	6 / 20	(*Z*)-**5a**	0.2: 99.8
2	(*Z*)-**5a**	5	6 / 20 then 2 / 50 then 4 / 63	(*E*)(*Z*)-**5a**	21: 77
3	(*Z*)-**5b**	5	5 / 20	(*E*)(*Z*)-**5b**	9: 91
4	(*E*)-**5b**	1	10 / 20	(*E*)(*Z*)-**5b**	30: 70
5	(*Z*)-**5c**	5	10 / 20	(*Z*)-**5c**	< 0.1: > 99.9
6	(*Z*)-**5c**	5	5 / 63	(*E*)(*Z*)-**5c**	37: 63
7	(*Z*)-**5d**	5	6 / 20 then 2 / 50 then 4 / 63	(*Z*)-**5d**	< 0.1: > 99.9
8	(*Z*)-**5e**	5	6 / 20 then 2 / 50 then 4 / 63	(*E*)(*Z*)-**5e**	2: 98
9	(*Z*)-**5f**	5	6 / 20	(*Z*)-**5f**	0.5: 99.5
10	(*Z*)-**5f**	5	6 / 20 then 2 / 50 then 4 / 63	(*E*)(*Z*)-**5f**	77: 23
11	(*Z*)-**5g**	5	6 / 20 then 2 / 50	(*Z*)-**5g**	< 0.1: > 99.9
12	(*Z*)-**5g**	5	6 / 20 then 2 / 50 then 4 / 63	(*E*)(*Z*)-**5g**	9: 91

a) These reactions were performed using 0.12 M benzene solutions of compounds (*Z*)- or (*E*)-**5**.

In preliminary experiments compounds (*E*)-**5c**, (*Z*)-**5c**, (*E*)-**5f** and (*Z*)-**5f** were tested at 27 °C at concentrations as low as 0.5 x 10^{-4} M for periods of time until 15 days and these tests were performed according to the same procedure previously employed to evaluate the bioactivity of some 2-aryl substituted methyl (*E*)-3-methoxypropenoates.[16,24] These tests showed that the bioactivity of (*E*)-**5c** was higher than that of (*E*)-**5f** and that (*Z*)-**5c** and (*Z*)-**5f** were less effective than the corresponding (*E*)-stereoisomers. All these compounds proved to be able to delay the growth of the tested fungal strains, but their bioactivity proved to be significantly lower than that of some 2-aryl substituted methyl (*E*)-3-methoxypropenoates which we had previously synthesized.[16,24]

In conclusion, a new convenient procedure for the synthesis of methyl 2-oxo-2-arylacetates **1** has been developed. This procedure, which involves the Pd-catalyzed reaction between arylzinc halides **9** (X = Cl, Br) and methyl oxalyl chloride **3d**, is clearly a significant improvement in terms of simplicity and efficiency over several procedures previously reported in the literature for the synthesis of α-ketoesters.[7,9,11,13,14] In these Pd-catalyzed reactions the best yields were obtained when the coupling reactions involved arylzinc bromides prepared from the corresponding aryl bromides by the procedure reported in the literature for the synthesis of functionalized organozinc halides via the corresponding organolithiums.[23] Compounds **1** were then converted into the corresponding methyl (*E*)- and (*Z*)-*O*-methyloximino-2-arylacetates (*E*)- and (*Z*)-**5**, whose structure and stereochemistry have been unambiguously assigned by NMR techniques. Compounds (*E*)-**5** so prepared included either a substance which is known to be a very important agrochemical fungicide, *i.e.* (*E*)-**5c**, as well as its fluorinated analogues, *i.e.* compounds (*E*)-**5g** and (*E*)-**5d**. It has also been observed that compounds (*Z*)-**5a**, (*E*)-**5b**, (*Z*)-**5c** and (*Z*)-**5f** undergo significant stereomutation in the presence of daylight and catalytic quantities of iodine. On the contrary compound (*Z*)-**5d** proved to be stereochemically stable under the experimental conditions used. Finally, it is also worth noting that some compounds among those of general formula (*E*)- and (*Z*)-**5** have been found to be able to delay the growth of fungal strains isolated from deteriorated papers, but they proved to be less effective than some previously synthesized 2-aryl substituted methyl (*E*)-3-methoxypropenoates.

EXPERIMENTAL

All melting points are uncorrected. Precoated plastic silica gel sheets Merck 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani data station 86.01. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m × 0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m × 0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as an internal standard, respectively. IR spectra were recorded on a Perkin-Elmer 1725-X FT-IR spectrophotometer. All reactions of air- and water-sensitive materials were performed in flame dried glassware under an atmosphere of argon or nitrogen. Air and water sensitive solutions were transferred with hypodermic syringes or double ended needles. Solvents were dried and distilled before use. The following compounds were prepared according to the literature: 1-bromo-2-

phenoxybenzene **10f**,[21] $Pd(PPh_3)_4$,[25] $PdCl_2(PPh_3)_2$.[26] THF slurries of 4-methoxyphenylzinc chloride **9a** (X = Cl), 4-chlorophenylzinc chloride **9b** (X = Cl), 2-2(2-methylphenoxymethyl)phenylzinc chloride **9c** (X = Cl) and 2-phenoxyphenylzinc chloride 9f (X = Cl) were prepared by reaction of THF solutions of the corresponding Grignard reagents with a THF slurry of 1.3 equiv of dry $ZnCl_2$ in THF (*Procedure A*). On the other hand, THF solutions of 4-methoxyphenylzinc bromide **9a** (X = Br), 2-[3-(trifluoromethyl)phenoxymethyl]phenylzinc bromide **9d** (X = Br), 2-[2-(trifluoromethyl)phenoxy]phenylzinc bromide **9e** (X = Br) and 2-[2-(trifluoromethyl)phenoxymethyl]phenylzinc bromide **9g** (X = Br) were prepared by the slow addition of a 1.6 M hexane solution of 1.05 equiv of butyllithium to solutions of the aryl bromides **10a**, **10d**, **10e** and **10g**, respectively, in a THF/Et_2O/hexane mixture (4 : 1 : 1) which was maintained at - 100 °C. After 12 - 25 min at - 100 °C a solution of 1.25 equiv od dry $ZnBr_2$ in THF was added and the resulting mixtures were allowed to warm up to room temperature (*Procedure B*).

1-Bromo-(2-methylphenoxymethyl)benzene ***10c.*** A solution of 2-bromobenzyl bromide **11** (12.50 g, 50.0 mmol) in dry acetone (11 ml) was added to a mixture of *o*-cresol **12a** (5.41 g, 50.0 mmol) and potassium carbonate (powder, 6.91 g, 50.0 mmol) in dry acetone (15 ml) and the resulting mixture was stirred under reflux for 2.5 h. It was then cooled to room temperature, concentrated under reduced pressure and the residue, which was diluted with water, was extracted repeatedly with Et_2O. The collected organic extracts were washed with water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using hexane as eluant, to give pure compound **10c** (12.85 g, 93 % yield) as a crystalline solid. M.p. 66-68 °C. MS, *m/z* (%): 278 (5), 276 (6), 197 (7), 171 (94), 169 (100), 107 (3), 90 (41), 78 (7), 77 (17). IR (KBr): ν 1495, 1250, 1124, 1057, 1024, 746 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.65 - 7.50 (2H, m, Harom), 7.40 - 7.05 (4H, br m, Harom), 6.95 - 6.80 (2H, m, Harom), 5.12 (2H, s, CH_2), 2.32 ppm (3H, s, CH_3). Anal. Calc for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Foud: C, 60.42; H, 4.68.

1-Bromo-2-[3-(trifluoromethyl)phenoxymethyl]benzene ***10d.*** The crude reaction product, which was obtained by reaction of α,α,α-trifluoro-*m*-cresol **12b** (8.11 g, 50.0 mmol) with 2-bromobenzyl bromide **11** (12.47 g, 50.0 mmol) and K_2CO_3 (6.91 g, 50.0 mmol) in dry acetone (55 ml) under reflux for 7 h according to a procedure very similar to that employed for the synthesis of **10c**, was purified by MPLC on silica gel, using hexane as eluant, to give pure **10d** (15.88 g, 96 % yield) as a low melting solid. M.p. 26-27.5 °C. MS, *m/z* (%): 332 (3), 330 (3), 172 (8), 171 (100), 169 (92), 133 (4), 113 (6), 90 (62), 75 (6). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.68-7.08 (8H, br m, Harom), 5.14 ppm (2H, s, CH_2). Anal. Calc for $C_{14}F_3H_{10}BrO$: C, 50.75; H, 3.04. Found: C, 50.33; H, 2.97.

1-Bromo-2-[2-(trifluoromethyl)phenoxymethyl]benzene ***10g.*** The crude reaction product, which was obtained by reaction of α,α,α-trifluoro-*o*-cresol **12c** (3.98 g, 24.6 mmol) with 2-bromobenzyl bromide **11** (6.12 g, 24.6 mmol) and K_2CO_3 (3.39 g, 24.6 mmol) in dry acetone (25 ml) under reflux for 6 h according to a procedure very similar to that employed for the synthesis of **10c**, was purified by MPLC on silica gel, using hexane as eluant, to give 99 % chemically pure **10g** (9.83 g, 97 % yield) as a crystalline solid. M.p. 78.5-80.5 °C. MS, *m/z* (%): 332 (1), 330 (2), 172 (7), 171 (100), 170 (7), 160 (89), 113 (4), 90 (51), 63 (15). IR (KBr)): ν 1325, 1262, 1126, 1113, 1037, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.69-7.40 (4H, br m, Harom), 7.36 (1H, *pseudo*-t, *J* = 7.2 Hz, H-4 or H-5 or H-4' or H-5'), 7.18 (1H, *pseudo*-t, *J* = 7.2 Hz, H-5 or H-4 or H-5' or H-4'),

7.20-6.93 (2H, m, Harom), 5.22 ppm (2H, s, CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz): 156.1, 135.6, 133.4, 132.4, 129.2, 128.2, 127.8, 127.3, 126.5, 121.4, 121.1, 120.6, 113.2, 69.6 ppm. Anal. Calc for $C_{14}F_3H_{10}BrO$: C, 50.75; H, 3.04. Found: C, 50.51; H, 2.90.

1-Bromo-2-[3-(trifluoromethyl)phenoxy]benzene ***10e***. α,α,α-Trifluomethyl-*m*-cresol **12b** (9.73 g, 60.0 mmol), 1,2-dibromobenzene **13** (7.08 g, 30.0 mmol) and ethyl acetate (0.146 ml, 1.50 mmol) were added under an argon atmosphere to a deareated and stirred mixture of molecular sieves 5Å (7.5 g), Cs_2CO_3 (19.55 g, 60.0 mmol), $(CuOTf)_2{\cdot}C_6H_6$ (0.377 g, 0.75 mmol) and 1-naphthoic acid (7.23 g, 42.0 mmol) in dry toluene (24 ml) and the resulting mixture, which was periodically monitored by GLC, was maintained at 110 °C for 9 days. The mixture was then cooled to 20 °C, diluted with toluene and filtered. The remaining molecular sieves were stirred for 0.5 h with another portion of toluene and the mixture was filtered. The collected filtrates were washed with a diluted aqueous NaOH solution and brine, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using hexane as eluant, to give 97 % chemically pure **10e** (5.01 g, 53 % yield) as a colourless liquid. MS, *m/z* (%): 318 (44), 316 (41), 237 (24), 217 (100), 168 (57), 145 (11), 95 (11), 76 (14), 75 (26). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.65 (1H, dd, J = 7.9 and 1.4 Hz, H-2 or H-5 or H-6' or H-4'), 7.42 (1H, *pseudo*-t, J = 7.7 Hz, H-4 or H-3 or H-5'), 7.38-7.24 (2H, m, Harom), 7.20 (1H, br s, H-2'), 7.16-6.98 ppm (3H, br m, Harom). Anal. Calc for $C_{13}F_3H_8BrO$: C, 49.24; H, 2.54. Found: C, 49.65; H, 2.52.

1-Bromo-2-(pentafluorophenoxy)benzene ***10h***. *o*-Bromophenol **14** (6.06 g, 35.0 mmol) and hexafluorobenzene **17** (16.93 g, 91.0 mmol) were added to a deareated mixture of $(CuOTf)_2{\cdot}C_6H_6$ (0.44 g, 0.88 mmol) and Cs_2CO_3 (11.40 g, 35.0 mmol) in dry pyridine (21 ml) and the resulting mixture, which was periodically monitored by GLC, was maintained under argon at 110 °C for 7 h. It was then cooled to 20 °C, diluted with toluene and washed repeatedly with cold 4 % aqueous HCl. The organic phase was then dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using hexane as eluant, to give 96 % chemically pure **10h** (7.50 g, 63 % yield) as a colourless liquid. MS, *m/z* (%): 340 (25), 338 (26), 259 (30), 231 (52), 157 (40), 117 (26), 93 (14), 76 (81), 75 (100). IR (film): ν 1518, 1475, 1222, 1047, 1021, 1001 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.63 (1H, d, J = 7.7 Hz, H-3 or H-6), 7.23 (1H, *pseudo*-t, J = 7.8 Hz, H-5 or H-4), 7.01 (1H, *pseudo*-t, J = 7.7 Hz, H-4 or H-5), 6.72 ppm (1H, d, J = 7.8 Hz, H-6 or H-3). Anal. Calc for $C_{12}F_5H_4BrO$: C, 42.51; H, 1.19. Found: C, 42.83; H, 1.10.

General procedure for the Pd-catalyzed cross-coupling reactions between methyl oxalyl chloride ***3d*** *and the arylzinc chlorides* ***9a-c*** *(X = Cl) and* ***9f*** *(X = Cl) prepared according to Procedure A.*. A THF slurry of an organozinc chloride **9** (X = Cl) was prepared by addition of a 0.43 M solution of the corresponding Grignard reagent (45.4 ml, 19.5 mmol) to a slurry of dry $ZnCl_2$ (3.45 g, 25.3 mmol) in THF, which was stirred at 0 °C. After stirring for 15 min at 0 °C and for 10 min at 20 °C, $Pd(PPh_3)_4$ (0.94 g, 0.82 mmol) was added. The mixture was then cooled to 0 °C and **3d** (1.49 ml, 16.3 mmol) was quickly added. The resulting mixture, which was periodically monitored by GLC, was stirred at 0 °C for the period of time reported in Table 1 and hydrolyzed at 0 °C with a cold saturated aqueous NH_4Cl solution. After usual workup, the crude reaction product was diluted with the solvent which was subsequently used for its purification by MPLC on silica gel and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel. Compounds **1a**, **1b**, **1c** and **1f** were prepared according to this procedure (entries 1, 3, 4 and 7, Table 1).

Methyl 2-oxo-2-(4-methoxy)phenylacetate ***1a***. The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and 4-methoxyphenylzinc chloride **9a** (X = Cl) according to the above mentioned procedure (entry 1, Table 1), was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (75 : 25) as eluant, to give in 52 % yield chemically pure **1a** as a colouress solid. M.p. 49-50.5 °C. MS, *m/z* (%): 194 (2), 137 (1), 136 (10), 135 (100), 107 (12), 104 (1), 92 (23), 77 (20), 73 (3). IR (KBr): ν 1732, 1672, 1600, 1268, 1220, 1168 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.01 (2H, dm, *J* = 8.9 Hz, Harom), 6.98 (2H, dm, *J* = 8.9 Hz, Harom), 3.96 (3H, s, OCH_3), 3.90 ppm (3H, s, OCH_3). Anal. Calc for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.92; H, 5.50.

Mtehyl 2-oxo-2-(4-chloro)phenylacetate ***1b***. The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and 4-chlorophenylzinc chloride **9b** (X = Cl), was purified by MPLC on silica gel, using a mixture of benzene and hexane (55 : 45) as eluant, to give in 60 % yield chemically pure **1b** as a pale yellow solid. M.p. 58-60 °C. MS, *m/z* (%): 198 (1), 141 (32), 140 (7), 139 (100), 113 (14), 111 (45), 76 (6), 75 (21), 74 (7). IR (KBr): ν 1729, 1685, 1588, 1214, 1171, 1005 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.00 (2H, d, *J* = 8.6 Hz, Harom), 7.49 (2H, d, *J* = 8.6 Hz, Harom), 3.98 ppm (3H, s, OCH_3). Anal. Calc for $C_9H_7ClO_3$: C, 54.43; H, 3.55. Found: C, 54.30; H, 3.37.

Methyl 2-oxo-2-[2-methylphenoxymethyl]phenylacetate ***1c.*** The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and 2-(2-methoxyphenoxymethyl)phenylzinc chloride **9c** (X = Cl) according to the above mentioned procedure (entry 4, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and hexane (60 : 40) as eluant, to give in 61 % yield chemically pure **1c** as a colourless oil which crystallized after several days at room temperature. M.p. 53-55 °C. MS, *m/z* (%): 284 (1), 225 (10), 178 (13), 177 (100), 149 (56), 119 (40), 118 (22), 91 (74), 77 (21). IR (film): ν 1737, 1687, 1495, 1242, 1204, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.95-7.80 (2H, m, H-4' and H-6'), 7.74 (2H, d, *J* = 7.7 Hz, H-6 and H-3), 7.64 (1H, *pseudo*-t, *J* = 7.7 Hz, H-5 or H-4), 7.44 (1H, *pseudo*-t, *J* = 7.7 Hz, H-4 or H-5), 7.25-7.08 (2H, m, H-3' and H-5'), 5.39 (2H, s, CH_2), 3.80 (3H, s, OCH_3), 2.29 ppm (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 187.9, 163.6, 156.2, 140.7, 134.0, 132.3, 130.8, 130.5, 127.5, 127.4, 127.0, 126.9, 121.0, 111.3, 68.0, 52.7, 16.4 ppm. Anal. Calc for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.65; H, 5.53.

Methyl 2-oxo-2-phenoxyphenylacetate ***1f.*** The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and 2-(phenoxy)phenylzinc chloride **9f** (X = Cl) according to the above mentioned procedure (entry 7, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and hexane (70 : 30) as eluant, to give in 74 % yield chemically pure **1f** as an oil. MS, *m/z* (%): 256 (2), 197 (100), 168 (8), 141 (10), 139 (8), 121 (3), 115 (22), 77 (19), 76 (4). IR (film): ν 1746, 1600, 1477, 1264, 1233, 1205 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.95 (1H, d, *J* = 7.8 Hz, H-3 or H-6), 7.52 (1H, t, *J* = 7.3 Hz, H-4'), 7.38 (2H, t, *J* = 7.8 Hz, H-4 and H-5), 7.20 (2H, *pseudo*-t, *J* = 7.3 Hz, H-3' and H-5'), 7.06 (2H, d, *J* = 7.3 Hz, H-2' and H-6'), 6.86 (1H, d, *J* = 7.8 Hz, H-6 or H-3), 3.69 ppm (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 185.9, 165.0, 158.3, 155.4, 135.9, 130.5, 130.0 (2 carbons), 124.6, 123.4, 119.4 (2 carbons), 118.0, 117.8, 52.3 ppm. Anal. Calc for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.20; H, 4.53.

General procedure for the Pd-catalyzed cross-coupling reactions between methyl oxalyl chloride ***3d*** *and the arylzinc bromide* ***9a*** *(X = Br),* ***9d,e*** *(X = Br) and* ***9g*** *(X = Br) prepared according to Procedure B.* A 1.74 M

solution of butyllithium in hexane (8.98 ml, 15.6 mmol) was added during 5 min to a solution of an aryl bromide (**10a**, **10d**, **10e** or **10g**) (15.0 mmol) in a mixture of THF/Et_2O/hexane (4: 1 :1) (72 ml) maintained under argon at - 100 °C and the resulting mixture was stirred for 12-25 min at - 100 °C. A solution of dry $ZnBr_2$ (4.22 g, 18.7 mmmol) in THF (30 ml) was added to - 100 °C and the resulting mixture was allowed to warm up to 20 °C. $Pd(PPh_3)_4$ (0.72 g, 0.63 mmol) was added, the mixture was cooled to 0 °C and **3d** (1.53 g, 12.5 mmol) was quickly added. The resulting mixture, which was periodically monitored by GLC, was stirred at 0 °C for the period of time reported in Table 1 and hydrolyzed at 0 °C with a cold saturated aqueous NH_4Cl solution.. After usual workup, the crude reaction product was diluted with the solvent which was subsequently used for its purification by MPLC on silica gel and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel. Compounds **1a**, **1d**, **1e** and **1g** were prepared according to this procedure (entries 2, 5, 6 and 8, Table 1).

Methyl 2-oxo-2-(4-methoxy)phenylacetate ***1a***. The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and **9a** (X = Br) according to this general procedure (entry 2, Table 1), was purified by MPLC on silica gel, using benzene as eluant, to give chemically pure **1a** in 91 % yield. The physical and spectral properties of this compound were in agreement with those of **1a** prepared from **3d** and **9a** (X = Cl).

Methyl 2-oxo-2-[3-(trifluoromethyl)phenoxymethyl]phenylacetate ***1d***. The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and 2-[3-(trifluorometyl)phenoxymethyl]phenylzinc bromide **9d** (X = Br) according to the above mentioned procedure (entry 5, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and hexane (60 : 40) as eluant, to give in 91 % yield chemically pure **1d** as a viscous oil. MS, *m/z* (%): 338 (1), 279 (20), 177 (79), 149 (46), 119 (32), 118 (35), 90 (100), 89 (56), 77 (9). IR (film): ν 1741, 1688, 1330, 1207, 1170, 1125 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.828 (1H, dd, *J* = 7.4 and 1.5 Hz, H-6), 7.771 (1H, d, *J* = 7.4 Hz, H-3), 7.666 (1H, ddd, *J* = 7.4, 7.4 and 1.5 Hz, H-4), 7.486 (1H, dd, *J* = 7.4 and 7.4 Hz, H-5), 7.410 (1H, dd, *J* = 8.2 and 8.2 Hz, H-5'), 7.248 (1H, d, *J* = 8.2 Hz, H-4'), 7.231 (1H, s, H-2'), 7.140 (1H, dd, *J* = 8.2 and 2.2 Hz, H-6'), 5.451 (2H, s, CH_2), 3.878 ppm (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 187.89 (C=O), 163.63 (O=C-O), 158.22 (C-1'), 139.47 (C-2), 134.16 (C-4), 132.46 (C-6), 132.03 (q, J_{C-F} = 32.9 Hz, C-3'), 130.45 (C-1), 130.13 (C-5'), 127.80 (C-5), 127.58 (C-3), 123.89 (q, J_{C-F} = 273.21 Hz, CF_3), 118.02 (C-4'), 117.95 (C-6'), 112.00 (C-2'), 68.40 (CH_2), 52.95 ppm (OCH_3). Anal. Calc for $C_{17}F_3H_{13}O_4$: C, 60.36; H, 3.87. Found: C, 60.03; H, 3.82.

Methyl 2-oxo-2-[3-(trifluoromethyl)phenoxy]phenylacetate ***1e***. The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and 2-[3-(trifluoromethyl)phenoxy]phenylzinc bromide **9e** (X = Br) according to the above mentioned procedure (entry 6, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and hexane (70 : 30) as eluant, to give in 84 % yield chemically pure **1e** as a viscous oil. MS, *m/z* (%): 324 (1), 265 (100), 245 (14), 217 (10), 168 (12), 139 (9), 95 (7), 92 (14), 75 (10). IR (film): ν 1746, 1452, 1330, 1265, 1175, 1130 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.993 (1H, dd, *J* = 7.6 and 1.7 Hz, H-6), 7.581 (1H, ddd, *J* = 8.4, 7.6 and 1.7 Hz, H-4), 7.511 (1H, dd, *J* = 8.0 and 8.0 Hz, H-5'), 7.458 (1H, d, *J* = 8.0 Hz, H-4'), 7.326 (1H, s, H-2'), 7.291 (1H, ddd, *J* = 7.6, 7.6 and 0.9 Hz, H-5), 7.238 (1H, dd, *J* = 8.0 and 1.9 Hz, H-6'), 6.897 (1H, d, *J* = 8.4 Hz, H-3), 3.699 ppm (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 185.64

(C=O), 164.81 (O=C-O), 157.27 (C-2), 156.05 (C-1'), 136.12 (C-4), 132.67 (C-3'), 131.11 (C-6), 130.74 (C-5'), 125.32 (C-1), 124.46 (C-5), 123.45 (q, J_{C-F} = 271.80 Hz, CF_3), 122.49 (C-6'), 121.30 (q, J_{C-F} = 3.81 Hz, C-4'), 118.38 (C-3), 116.25 (q, J_{C-F} = 38.1 Hz, C-2'), 52.54 ppm (OCH_3). Anl. Calc for $C_{16}F_3H_{11}O_4$: C, 59.27; H, 3.42. Found: C, 58.98; H, 3.41.

Methyl 2-oxo-2-[2-(trifluoromethyl)phenoxymethyl]phenylacetate ***1g***. The crude reaction product, which was obtained from the Pd-catalyzed reaction between **3d** and 2-[2)(trifluoromethyl)phenoxymethyl]phenylzinc bromide **9g** (X = Br) according to the above mentioned procedure (entry 8, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and hexane (60 : 40) as eluant, to give in 91 % yield chemically pure **1g** as a crystalline solid. M.p. 77-79 °C. MS, *m/z* (%): 338 (1), 279 (13), 177 (66), 149 (40), 137 (8), 133 (9), 119 (32), 90 (100), 89 (66). IR (KBr): ν 1737, 1326, 1276, 1210, 1126, 1058 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.014 (1H, d, *J* = 7.9 Hz, H-5), 7.850 (1H, dd, *J* = 7.9 and 0.8 Hz, H-2), 7.729 (1H, ddd, *J* = 7.9, 7.9 and 0.8 Hz, H-4), 7.625 (1H, dd, *J* = 7.5 and 1.2 Hz, H-3'), 7.511 (1H, m, H-5'), 7.486 (1H, m, H-3), 7.125 (1H, d, *J* = 8.3 Hz, H-6'), 7.045 (1H, dd, *J* = 7.5 and 7.5 Hz, H-4'), 5.567 (2H, s, CH_2), 3.983 ppm (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 188.19 (C=O), 164.29 (O-C=O), 156.12 (C-1'), 140.42 (C-6), 134.96 (C-4), 133.48 (C-5'), 132.83 (C-2), 128.91 (C-1), 127.44 (C-3), 127.40 (C-5), 127.22 (q, J_{C-F} = 4.7 Hz, C-3'), 123.84 (q, J_{C-F} = 271.14, CF_3), 120.58 (C-4'), 118.93 (q, J_{C-F} = 30.51 Hz, C-2'), 113.17 (C-6'), 68.41 (CH_2), 52.90 ppm (OCH_3). Anal. Calc for $C_{17}F_3H_{13}O_4$: C, 60.36; H, 3.87. Found: C, 60.47; H, 4.17.

General procedure for the synthesis of methyl (E)- and (Z)-O-methyloximino-2arylacetates of general formula (E)- and (Z)-5. A molar excess of *O*-methylhydroxylamine hydrochloride **20** (2.8 - 4.0 equiv) was added to a solution of a compound of general formula **1** (6.8 mmol) in dry pyridine (30 ml) and the resulting mixture was stirred under argon for the period of time and at the temperature reported in Table 2. This table also summarizes the **20**: **1** molar ratios used in the preparation of compounds (*E*)- and (*Z*)-**5** according to this general procedure. The progress of the reaction was monitored by GLC analysis. The reaction mixture was then concentrated *in vacuo* and the residue, which was diluted with Et_2O, was washed repeatedly with water, dried and concentrated *in vacuo*. Purification of the residue by MPLC on silica gel allowed to obtain chemically and stereoisomerically pure compounds (*Z*)- and (*E*)-**5**. Compounds (*E*)- and (*Z*)-**5a-g** were prepared according to this general procedure.

Methyl (E)- and (Z)-O-methyloximino-2-(4-methoxy)phenylacetate (E)- and (Z)-5a. A GLC analysis of the crude reaction product, which was obtained from the reaction between **20** and **1a** according to the above mentioned procedure (entry 1, Table 2), showed the presence of two components in a 17 : 83 molar ratio. This crude product was purified by MPLC on silica gel using benzene as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 56 % yield the chemically and stereoisomerically pure major component. This compound, which was shown to be (*Z*)-**5a**, had: m.p. 60-62 °C. MS, *m/z* (%): 223 (26), 164 (19), 148 (6), 134 (10), 133 (100), 103 (14), 92 (7), 90 (20), 77 (14). IR (KBr): ν 1724, 1719, 1294, 1071, 1029, 1020 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.494 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 6.913 (2H, d, *J* = 8.9 Hz, H-3 and H-5), 3.991 (3H, s, $NOCH_3$), 3.929 (3H, s, $COOCH_3$), 3.824 ppm (3H, s, $ArOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.31 (C=O), 161.37 (C-4), 150.26 (C=N), 127.75 (C-2), 127.75 (C-6), 122.63 (C-1), 114.27 (C-3), 114.27 (C-5), 62.82 ($NOCH_3$), 55.35 ($ArO\underline{CH_3}$), 52.31 ppm ($COO\underline{CH_3}$). A NOESY experiment

showed the presence of an intense cross-peak between the resonances of H-2 and H-6 and that of the $COOCH_3$ protons as well as a cross-peak of lower intensity between the resonances of H-2 and H-6 and that of the $NOCH_3$ protons. Anal. Calc for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87. Found: C, 59.60; H, 6.22.

Concentration of the last eluted chromatographic fractions allowed to isolate the minor component of the crude reaction mixture in 12 % yield. This compound, which was shown to be (*E*)-**5a**, had: m.p. 43-45 °C. MS, *m/z* (%): 223 (24), 164 (16), 148 (6), 134 (12), 133 (100), 103 (17), 92 (7), 90 (23), 77 (15). IR (KBr): ν 1724, 1719, 1294, 1071, 1029, 1020 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.451 (2H, d, *J* = 8.9 Hz, H-6 and H-2), 6.931 (2H, d, *J* = 8.9 Hz, H-3 and H-5), 4.061 (3H, s, $NOCH_3$), 3.892 (3H, s, $COOCH_3$), 3.834 ppm (3H, s, $ArOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.25 (C=O), 160.37 (C-4), 148.62 (C=N), 131.05 (C-2), 131.05 (C-6), 121.44 (C-1), 113.35 (C-3), 113.35 (C-5), 63.61 ($NOCH_3$), 55.28 ($ArO\underline{CH_3}$), 52.94 ppm ($COO\underline{CH_3}$). A NOESY experiment showed the presence of an intense cross-peak between the resonances of H-2 and H-6 and that of the $NOCH_3$ protons as well as a cross-peak of lower intensity between the resonances of H-2 and H-6 and that of the $COOCH_3$ protons. Anal. Calc for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87. Found: C, 59.58; H, 6.21.

*Methyl (E)- and (Z)-O-methyloximino-2-(4-chloro)phenylacetate (E) and (Z)-**5b**.* A GLC analysis of the crude reaction product, which was obtained from the reaction between **20** and **1b** according to the above mentioned procedure (entry 2, Table 2), showed the presence of two components in a 28 : 72 molar ratio. This crude product was purified by MPLC on silica gel using a mixture of hexane and Et_2O (90 : 10) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 63 % yield the chemically and stereoisomerically pure major component. This compound, which corresponded to (*Z*)-**5b**, had: m.p. 41-43 °C. MS, *m/z* (%): 227 (45), 170 (19), 168 (67), 155 (30), 153 (100), 137 (82), 111 (27), 102 (49), 75 (38). IR (film): ν 1742, 1494, 1094, 1054, 1027, 1014 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.496 (2H, d, *J* = 8.8 Hz, H-2 and H-6), 7.357 (2H, d, *J* = 8.8 Hz, H-3 and H-5), 4.020 (3H, s, $NOCH_3$), 3.937 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.55 (C=O), 149.29 (C=N), 136.32 (C-4), 128.93 (C-3), 128.93 (C-5), 128.55 (C-1), 127.34 (C-2), 127.34 (C-6), 62.99 ($NOCH_3$), 52.33 ppm ($COO\underline{CH_3}$). Anal. Calc for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43. Found: C, 53.00; H, 4.70.

Concentration of the last eluted chromatographic fractions allowed to isolate in 24 % yield the minor component of the crude reaction product. This chemically and stereoisomerically pure compound, which corresponded to (*E*)-**5b**, had: m.p. 72-74 °C. MS, *m/z* (%): 227 (50), 170 (20), 168 (66), 155 (32), 153 (100), 137 (94), 111 (30), 102 (60), 75 (44). IR (KBr): ν 1727, 1214, 1090, 1070, 1027, 1010 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.396 (2H, m, H-2 and H-6), 7.372 (2H, m, H-3 and H-5), 4.066 (3H, s, $NOCH_3$), 3.892 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.45 (C=O), 147.89 (C=N), 135.60 (C-4), 130.54 (C-3), 130.54 (C-5), 128.19 (C-2), 128.19 (C-6), 127.49 (C-1), 63.73 ($NOCH_3$), 52.94 ppm ($COO\underline{CH_3}$). Anal. Calc for $C_{10}H_{13}ClNO_3$: C, 52.76; 4, 4.43. Found: C, 52.44; H, 4.15.

*Methyl (E)- and (Z)-O-methyloximino-2-](2-methyl)phenoxymethyl]phenylacetate (E)- and (Z)-**5c**.* A GLC analysis of the crude reaction product, which was obtained from the reaction between **20** and **1c** according to the above mentioned general procedure (entry 3, Table 2), showed the presence of two components in a 69 : 31 molar ratio. This crude product was purified by MPLC on silica gel using a mixture of benzene and hexane (60 : 40) as eluant. Concentration of the eluted chromatographic fractions allowed to isolate in 28 % yield the chemically and stereoisomerically pure minor component of the crude reaction product. This compound, which

was shown to be (Z)-**5c**, had: m.p. 53-55 °C. MS, *m/z* (%): 282 (2), 206 (100), 175 (14),146 (34), 132 (19), 116 (83), 107 (14), 89 (30), 77 (36). IR (film): ν 1742, 1495, 1243, 1226, 1049, 1021 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.743 (1H, d, *J* = 7.6 Hz, H-3), 7.460 (1H, dd, *J* = 7.6 and 7.6 Hz, H-4), 7.395 (1H, d, *J* = 7.6 Hz, H-6), 7.360 (1H, dd, *J* = 7.6 and 7.6 Hz, H-5), 7.180 (1H, d, *J* = 7.5 Hz, H-3'), 7.147 (1H, dd, *J* = 7.5 and 7.5 Hz, H-5'), 6.884 (1H, dd, *J* = 7.5 and 7.5 Hz, H-4'), 6.840 (1H, d, *J* = 7.5 Hz, H-6'), 5.313 (2H, br s, CH_2), 4.004 (3H, s, $NOCH_3$), 3.882 (3H, s, $COOCH_3$), 2.334 ppm (3H, s, Ar-CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.67 (C=O), 156.76 (C-1'), 150.59 (C=N), 136.98 (C-2), 130.72 (C-3'), 130.07 (C-4), 128.90 (C-6), 127.94 (C-3), 127.54 (C-1), 127.54 (C-5), 126.94 (C-2'), 126.79 (C-5'), 120.54 (C-4'), 111.23 (C-6'), 68.00 (CH_2), 63.18 ($NOCH_3$), 52.43 ($COO\underline{CH_3}$), 16.43 ppm ($ArCH_3$). A NOESY experiment showed the presence of a cross-peak between the resonance of the $NOCH_3$ protons and that of H-6'. On the contrary, there was no cross-peak between the resonance of the $NOCH_3$ protons and that for H-6, which was present in the stereoisomer of this compound. Anal. Calc for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11. Found: C, 68.60; H, 5.90.

The chromatographic column was then eluted with benzene and concentration of the eluted chromatographic fractions allowed to isolate chemically and stereoisomerically pure (*E*)-**5c** in 63 % yield. M.p. 98 -100 °C. MS, *m/z* (%): 282 (2), 206 (30), 131 (33), 117 (19), 116 (100), 107 (13), 91 (21), 89 (29), 77 (32). IR (KBr): ν 1737, 1238, 1067, 1019, 1008, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.585 (1H, dd, *J* = 7.7 and 1.4 Hz, H-3), 7.448 (1H, ddd, *J* = 7.7, 7.7 and 1.4 Hz, H-6), 7.387 (1H, ddd, *J* = 7.7, 7.7 and 1.4 Hz, H-5), 7.209 (1H, dd, *J* = 7.7 and 1.4 Hz, H-6), 7.140 (1H, d, *J* = 8.2 Hz, H-3'), 7.102 (1H, dd, *J* = 8.2 and 8.2 Hz, H-5'), 6.858 (1H, dd, *J* = 8.2 and 8.2 Hz, H-4'), 6.775 (1H, d, *J* = 8.2 Hz, H-6'), 4.959 (2H, s, CH_2), 4.029 (3H, s, $NOCH_3$), 3.823 (3H, s, $COOCH_3$), 2.252 ppm (3H, s, $ArCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.27 (C=O), 156.60 (C-1'), 149.37 (C=N), 135.78 (C-2), 130.73 (C-3'), 130.51 (C-2'), 129.62 (C-4), 128.52 (C-6), 127.69 (C-3), 127.69 (C-5), 127.00 (C-1), 126.71 (C-5'), 120.69 (C-4'), 111.29 (C-6'), 68.08 (CH_2), 63.82 ($NOCH_3$), 52.93 ($COO\underline{CH_3}$), 16.23 ppm ($ArCH_3$). Anal. Calc for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11. Found: C, 68.79; H, 5.88.

*Methyl (E)- and (Z)-O-methyloximino-2-[3-(trifluoromethyl)phenoxymethyl]phenylacetate (E)- and (Z)-**5d**.* A GLC analysis of the crude rection product, which was obtained from the reaction between **20** and **1d** according to the above mentioned procedure (entry 4, Table 2), showed the presence of two components in a 75 : 25 molar ratio. This crude product was purified by MPLC on silica gel using a mixture of hexane and Et_2O (80 : 20) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 25 % yield chemically and stereoisomerically pure (Z)-**5 d** as a crystalline solid. M.p. 63-65 °C. MS, *m/z* (%): 336 (21), 206 (100), 175 (56), 143 (32), 132 (26), 116 (98), 91 (17), 90 (22), 89 (56). IR (KBr): ν 1739, 1341, 1329, 1231, 1164, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.677 (1H, d, *J* = 7.7 Hz, H-3), 7.455 (1H, ddd, *J* = 7.7, 7.7 and 1.6 Hz, H-4), 7.409 (1H, m, H-6), 7.393 (1H, m, H-5'), 7.372 (1H, m, H-5), 7.226 (1H, m, H-4'), 7.215 (1H, br s, H-2'), 7.121 (1H, dd, *J* = 8.3 and 2.4 Hz, H-6'), 5.324 (2H, br s, CH_2), 3.953 (3H, s, $NOCH_3$), 3.886 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.58 (C=O), 158.76 (C-1'), 150.39 (C=N), 135.84 (C-2), 131.90 (q, $J_{C\text{-}F}$ = 36.30 Hz, C-3'), 130.25 (C-4), 130.25 (C-5'), 129.08 (C-6), 128.56 (C-3), 128.23 (C-1), 128.04 (C-5), 122.83 (q, $J_{C\text{-}F}$ = 272.12 Hz, CF_3), 118.19 (C-6'), 117.54 (C-4'), 111.78 (C-2'), 68.46 (CH_2), 63.19 ($NOCH_3$), 52.40 ppm ($COO\underline{CH_3}$). A NOESY experiment showed the absence of the cross-peak between the resonance of the $NOCH_3$ protons and that of H-6. On the contrary, this cross-peak was observed for the stereoisomer of this compound. Anal. Calc for $C_{18}F_3H_{16}NO_4$: C, 58.86; H, 4.39. Found: C, 58.68; H, 4.50.

Concentration of the last eluted chromatographic fractions allowed to isolate in 71 % yield chemically and stereoisomerically pure (*E*)-**5d** as a crystalline solid. M.p. 56-58 °C. MS, *m/z* (%): 336 (5), 206 (23), 146 (9), 132 (20), 131 (29), 116 (100), 105 (7), 91 (10), 90 (11). IR (KBr): ν 1741, 1342, 1240, 1117, 1068, 1013 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.519 (1H, d, *J* = 7.0 Hz, H-3), 7.446 (1H, ddd, *J* = 7.5, 7.5 and 1.5 Hz, H-4), 7.408 (1H, ddd, *J* = 7.5, 7.5 and 1.5 Hz, H-5), 7.363 (1H, dd, *J* = 8.2 and 8.2 Hz, H-5'), 7.222 (1H, d, *J* = 7.5 Hz, H-6), 7.206 (1H, d, *J* = 8.2 Hz, H-4'), 7.133 (1H, br s, H-2'), 7.049 (1H, dd, *J* = 8.2 and 2.5 Hz, H-6'), 4.987 (2H, br s, CH_2), 4.022 (3H, s, $NOCH_3$), 3.842 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.27 (C=O), 158.50 (C-1'), 149.38 (C=N), 134.53 (C-2), 131.86 (q, J_{C-F} = 31.80 Hz, C-3'), 129.99 (C-5'), 129.65 (C-4), 129.52 (C-1), 128.70 (C-6), 128.06 (C-5), 127.83 (C-3), 123.90 (q, J_{C-F} = 272.12 Hz, CF_3), 118.10 (C-6'), 117.78 (C-4'), 111.73 (C-2'), 68.67 (CH_2), 63.85 ($NOCH_3$), 52.98 ppm ($COO\underline{CH_3}$). Anal. Calc for $C_{18}F_3H_{16}NO_4$: C, 58.86; H, 4.39. Found: C, 58.48; H, 4.22.

Methyl (E)- and (Z)-O-methyloximino-2-[3-(trifluoromethyl)phenoxy]phenylacetate (E)- and (Z)-5e. A GLC analysis of the crude reaction product, which was obtained from the reaction between **20** and **1e** according to the above mentioned general procedure (entry 5, Table 2), showed the presence of two components in a 44 : 56 molar ratio. This crude product was purified by MPLC on silica gel using benzene and hexane (80 : 20) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 52 % yield chemically and stereoisomerically pure (*Z*)-**5e** as an oil. MS, *m/z* (%): 353 (30), 307 (85), 264 (64), 263 (100), 262 (77), 235 (52), 145 (93), 95 (72), 59 (86). IR (film): ν 1749, 1450, 1330, 1229, 1173, 1130 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.847 (1H, dd, *J* = 8.0 and 1.2 Hz, H-6), 7.433 (1H, dd, *J* = 8.1 and 8.1 Hz, H-5'), 7.400 (1H, m, H-4), 7.364 (1H, m, H-4'), 7.220 (1H, ddd, *J* = 8.0, 8.0 and 1.2 Hz, H-5), 7.201 (1H, s, H-2'), 7.105 (1H, dd, *J* = 8.1 and 2.0 Hz, H-6'), 6.893 (1H, dd, *J* = 8.0 and 1.2 Hz, H-3), 4.025 (3H, s, $NOCH_3$), 3.624 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.20 (C=O), 157.16 (C-1'), 153.71 (C-2), 147.23 (C=N), 132.29 (C-3'), 131.85 (C-4), 130.40 (C-5'), 129.38 (C-6), 124.81 (C-5), 123.74 (C-1), 123.58 (q, J_{C-F} = 271.80 Hz, CF_3), 121.37 (C-6'), 120.16 (C-4'), 119.64 (C-3), 115.10 (q, J_{C-F} = 3.8 Hz, C-2'), 63.24 ($NOCH_3$), 52.06 ppm ($COO\underline{CH_3}$). A NOESY experiment showed the absence of the cross-peak between the resonance of the $NOCH_3$ protons and that of H-6. On the contrary, this cross-peak was observed for the stereoisomer of this compound. Anal. Calc for $C_{17}F_3H_{14}NO_4$: C, 57.79; H, 3.99. Found: C, 58.06; H, 4.17.

Concentration of the last eluted chromatographic fractions allowed to isolate in 46 % yield chemically and stereoisomerically pure (*E*)-**5e** as an oil. MS, *m/z* (%): 353 (15), 307 (62), 264 (43), 263 (75), 262 (48), 235 (36), 145 (90), 75 (72), 59 (100). IR (film): ν 1731, 1449, 1330, 1237, 1172, 1129, 1072 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.320 (1H, m, H-5'), 7.300 (1H, m, H-4), 7.287 (1H, m, H-6), 7.245 (1H, d, *J* = 7.8 Hz, H-4'), 7.142 (1H, m, H-5), 7.115 (1H, s, H-2'), 7.076 (1H, dd, *J* = 7.8 and 2.2 Hz, H-6'), 6.870 (1H, dd, *J* = 8.2 and 0.7 Hz, H-3), 3.887 (3H, s, $NOCH_3$), 3.667 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.20 (C=0), 157.33 (C-1'), 153.64 (C-2), 146.62 (C=N), 132.11 (q, J_{C-F} = 32.7 Hz, C-3'), 131.13 (C-4), 130.79 (C-5'), 130.20 (C-6), 123.87 (C-5), 123.67 (q, J_{C-F} = 272.50 Hz, CF_3), 122.52 (C-1), 121.77 (C-6'), 119.93 (q, J_{C-F} = 3.63 Hz, C-4), 119.07 (C-3), 115.21 (C-2'), 63.64 ($NOCH_3$), 52.80 ppm ($COOCH_3$). Anal. Calc for $C_{17}F_3H_{14}NO_4$: C, 57.79; H, 3.99. Found: C, 58.19; H, 3.99.

Methyl (E)- and (Z)-O-methyloximino-2-(2-phenoxy)phenylacetate (E)- and (Z)-5f. A GLC analysis of the crude reaction product, which was obtained from the reaction between **20** and **1f** according to the above

mentioned general procedure (entry 6, Table 2), showed the presence of two components in a 45 : 55 molar ratio. This crude product was purified by MPLC on silica gel using benzene as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 53 % yield chemically and stereoisomrically pure (*Z*)-**5 f** as an oil. MS, *m/z* (%): 285 (7), 239 (72), 196 (22), 195 (50), 194 (55), 167 (44), 139 (12), 91 (16), 77 (100). IR (film): ν 1751, 1739, 1485, 1265, 1228, 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.832 (1H, dd, *J* = 7.9 and 1.6 Hz, H-6), 7.340 (1H, m, H-4), 7.321 (2H, m, H-5' and H-3'), 7.139 (1H, m, H-5), 7.110 (1H, m, H-4'), 6.963 (2H, m, H-2' and H-6'), 6.854 (1H, dd, *J* = 8.3 and 1.1 Hz, H-3), 4.034 (3H, s, $NOCH_3$), 3.633 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.44 (C=O), 156.59 (C-1'), 154.89 (C-2), 147.73 (C=N), 131.61 (C-4), 129.78 (C-3'), 129.78 (C-5') 128.95 (C-6), 123.74 (C-4'), 123.74 (C-5), 123.12 (C-1), 118.95 (C-3), 118.71 (C-6'), 118.71 (C-2'), 63.25 ($NOCH_3$), 51.80 ppm ($COO\underline{CH_3}$). Anal. Calc for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30. Found: C, 67.80; H, 5.60.

Concentration of the last eluted chromatographic fractions allowed to isolate in 41 % yield chemically and stereoisomerically pure (*E*)-**5 f** as a crystalline solid. M.p. 109 111 °C. MS, *m/z* (%): 285 (3), 239 (88), 196 (23), 195 (50), 194 (49), 167 (48), 139 (13), 91 (19), 77 (100). IR (KBr): ν 1735, 1483, 1246, 1219, 1068, 1011 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.382 (1H, dd, *J* = 7.4 and 1.5 Hz, H-6), 7.340 (1H, m, H-4), 7.312 (2H, dd, *J* = 8.6 and 7.4 Hz, H-5' and H-3'), 7.150 (1H, ddd, *J* = 7.4, 7.4 and 0.7 Hz, H-5), 7.099 (1H, ddd, *J* = 7.4, 7.4 and 1.1 Hz, H-4'), 6.999 (2H, dd, *J* = 8.6 and 1.1 Hz, H-2' and H-6'), 6.913 (1H, d, *J* = 8.6 Hz, H-3), 4.025 (3H, s, $NOCH_3$), 3.778 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.49 (C=O), 156.66 (C-1'), 154.75 (C-2), 146.99 (C=N), 130.88 (C-4), 130.62 (C-6), 129.63 (C-3'), 129.63 (C-5'), 123.61 (C-4'), 122.72 (C-5), 121.69 (C-1), 119.05 (C-6'), 119.05 (C-2'), 118.19 (C-3), 63.63 ($NOCH_3$), 52.81 ppm ($COO\underline{CH_3}$). A NOESY experiment showed the presence of a cross-peak between the resonance of the $NOCH_3$ protons and those of H-2' and H-6'. This cross-peak was not observed for the stereoisomer of this compound. Anal. Calc for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30. Found: C, 67.27; H, 5.50.

*Methyl (E)- and (Z)-O-methyloximino-2-[2-(trifluoromehyl)phenoxymethyl]phenylacetate (E)- and (Z)-***5g.** A GLC analysis of the crude reaction product, which was obtained from the reaction between **20** and **1 g** according to the above mentioned general procedure (entry 7, Table 2), showed the presence of two components in a 57 : 43 molar ratio. This crude product was purified by MPLC on silica gel using benzene as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 42 % yield chemically and stereoisomerically pure (*Z*)-**5 g** as a crystalline solid. M.p. 74-76 °C. MS, *m/z* (%): 336 (9), 206 (85), 175 (40), 143 (31), 132 (27), 117 (43), 116 (100), 90 (22), 89 (70). IR (KBr): ν 1773, 1325, 1279, 1235, 1126, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.806 (1H, d, *J* = 7.7 Hz, H-3), 7.611 (1H, d, *J* = 7.9 Hz, H-3'), 7.463 (1H, m, H-4), 7.457 (1H, m, H-5'), 7.352 (1H, m, H-5), 7.352 (1H, m, H-6), 7.020 (1H, dd, *J* = 7.9 and 7.9 Hz, H-4'), 5.426 (2H, s, CH_2), 4.042 (3H, s, $NOCH_3$), 3.917 ppm (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.67 (C=O), 156.33 (C-1'), 150.71 (C=N), 136.16 (C-2), 133.31 (C-5'), 130.34 (C-4), 128.70 (C-5), 128.70 (C-6), 128.22 (C-1), 127.61 (C-3'), 127.20 (C-3), 123.82 ($J_{C\text{-}F}$ = 272.48 Hz, CF_3), 120.21 ($J_{C\text{-}F}$ = 22.16 Hz, C-4'), 119.10 ($J_{C\text{-}F}$ = 31.24 Hz, C-2'), 113.14 ($J_{C\text{-}F}$ = 22.16 Hz, C-6'), 68.40 (CH_2), 63.27 ($NOCH_3$), 52.59 ppm ($COO\underline{CH_3}$). Anal. Calc for $C_{18}F_3H_{16}NO_4$: C, 58.86; H, 4.39. Found: C, 59.23; H, 4.24.

Concentration of the last eluted chromatographic fractions allowed to isolate in 56 % yield chemically and stereoisomerically pure (*E*)-**5 g** as a crystalline solid. M.p. 117-119 °C. MS, *m/z* (%): 336 (1), 206 (24), 133 (9), 132 (24), 131 (33), 117 (19), 116 (100), 90 (14), 89 (40). IR (KBr): ν 1726, 1326, 1226, 1125, 1112, 760

cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.630 (1H, d, J = 7.5 Hz, H-3), 7.585 (1H, dd, J = 7.7 and 0.9 Hz, H-3'), 7.454 (1H, m, H-4), 7.383 (1H, m, H-5), 7.190 (1H, m, H-6), 7.005 (1H, dd, J = 7.7 and 7.7 Hz, H-4'), 5.044 (2H, s, CH_2), 4.060 (3H, s, $NOCH_3$), 3.873 ppm (3H, s, $COO\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.25 (C=O), 156.28 (C-1'), 149.10 (C=N), 134.72 (C-2), 133.21 (C-5'), 129.86 (C-4), 128.53 (C-6), 128.17 (C-1), 127.67 (C-5), 127.13 (C-3), 127.13 (C-3'), 123.69 (q, $J_{C\text{-}F}$ = 272.48 Hz, CF_3), 120.38 (m, $J_{C\text{-}F}$ = 21.07 Hz, C-4'), 119.15 (q, $J_{C\text{-}F}$ = 30.52 Hz, C-2'), 113.31 ($J_{C\text{-}F}$ = 21.07 Hz, C-6'), 68.25 (CH_2), 63.90 ($NOCH_3$), 53.08 ppm ($COO\underline{CH_3}$). A NOESY experiment showed the presence of a cross-peak between the resonance of the $NOCH_3$ protons and that of H-6. This cross-peak was not observed for the stereoisomer of this compound. Anal. Calc for $C_{18}F_3H_{16}NO_4$: C, 58.86; H, 4.39. Found: C, 58.68; H, 3.92.

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