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Steric and Electronic Tuning of Chiral Bis(oxazoline) Ligands with 3,3′-Bithiophene Backbone

Maurizio Benaglia,*,† Tiziana Benincori,*,‡ Patrizia Mussini,§ Tullio Pilati,∥ Simona Rizzo,∥ and Franco Sannicolò†,∥,⊥

Dipartimento di Chimica Organica e Industriale dell'Università, via Golgi 19-20133 Milano, Italy, Dipartimento di Scienze Chimiche ed Ambientali dell'Università dell'Insubria, Via Valleggio, 11-22100 Como, Italy, Dipartimento di Chimica Fisica ed Elettrochimica dell'Università, via Golgi, 19-20133 Milano, Italy, Istituto CNR Scienze e Tecnologie Molecolari, via C. Golgi, 19-20133 Milan, Italy, and CIMAINA − Centro Interdisciplinare Materiali e Interfacce Nanostrutturati, Via Celoria, 16-20133 Milano, Italy

maurizio.benaglia@unimi.it; tiziana.benincori@uninsubria.it

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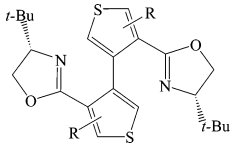

The role played by the electronic properties and the steric features of bis(oxazoline) ligands in the Cu(I)-catalyzed cyclopropanation of styrene effected with ethyl diazoacetate was investigated. Two pairs of new bis(oxazolines) displaying flexible and atropisomeric 3,3′-bithiophene backbones were synthesized and structurally and electronically characterized. For the first time, the electrochemical oxidative potential was used as a reliable index of the electronic density on the nitrogen atom of the chelating groups of new and, for comparative purposes, of already known bis(oxazolines). The Cu(I) complexes of the new ligands were prepared, and their enantioselection ability and catalytic efficiency were tested. This investigation suggests that steric factors and catalyst geometrical features are clearly more important than any consideration of the electronic properties of the chiral ligands.

Introduction

The class of C_2-symmetric ligands characterized by two chiral 2-(5-alkyl)oxazoline groups supported on the ortho,ortho′ positions of a biaryl scaffold has recently attracted some attention, due to the good results obtained in some specific asymmetric processes, like copper-catalyzed inter-[1] and intramolecular[2] cyclopropanation and asymmetric allylic oxidation,[3] where stereoselection levels comparable to those attainable with classical methylene bis(oxazolines) were reached.[4]

As expected, the energy barrier to rotation around the bond interconnecting the aromatic rings is a crucial parameter for the performance of these ligands. If rotation is not allowed, a new configurationally stable axial stereogenic element is generated in addition to the stereocenters present on the oxazoline rings, and consequently, two diastereoisomers, differing in the configuration of the stereogenic axis, are formed. The metal complexes of one of them, where there is matching of the configurations of the stereogenic elements, is expected to display higher stereoselection ability than the complex resulting from the mismatching arrangement.

* To whom correspondence should be addressed. (M.B.) Tel: +39.02.50314171. Fax: +39.02.50314159. (T.B.) Tel: +39.02.50314174. Fax: +39.02.50314139.

† Dipartimento di Chimica Organica e Industriale dell'Università.

‡ Dipartimento di Scienze Chimiche ed Ambientali dell'Università dell'Insubria.

§ Dipartimento di Chimica Fisica ed Elettrochimica dell'Università.

∥ Istituto CNR Scienze e Tecnologie Molecolari.

⊥ CIMAINA − Centro Interdisciplinare Materiali e Interfacce Nanostrutturati.

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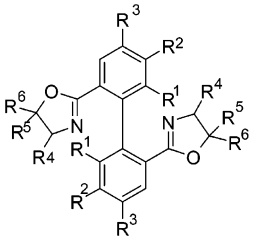
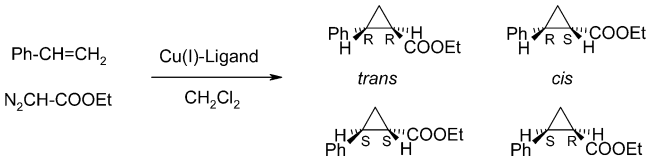
SCHEME 1. Atropisomeric Bisoxazolines with Biphenyl Backbone Carrying Substituents with Different Electronic and Steric Properties



1

R^1 = Me, MeO, Br
R^2 = H, MeO
R^3 = H
R^2, R^3 = C_8H_8
R^4 = Et, *i*-Pr, Ph, Me, *t*-Bu
R^5, R^6 = H, Ph

SCHEME 2. Cyclopropanation Reaction of Styrene with Ethyl Diazoacetate



The choice of biaryl backbones with unhindered rotation around the interanular bond as scaffolds for inherently chiral electron donor functions represents a quite recent trend in the design of new chiral chelating ligands for asymmetric catalysis.[5] The advantage of the ligands endowed with conformationally free biaryl backbones is related to the possibility that they could spontaneously assume in the metal complexes the arrangement favorably matching the configuration of the oxazolinic stereocenters. Alternatively, if both the diastereomeric metal complexes are formed, there is a well-grounded probability that the stereoisomer where axial and central configurations are matching would be more active than the one where mismatching occurs.

In the field of axially fixed C_2-symmetric 2,2′-bis(oxazolyl)-1,1′-biaryl systems, the most wide-scope search was developed by Rippert,[6] who tried to draw some conclusions on the electronic and steric requirements of the ligand to attain good stereoselection levels. An ample number of bis(oxazolines) **1** characterized by a biphenyl atropisomeric backbone carrying substituents with different electronic properties were synthesized and tested. A wide variety of alkyl substituents having different steric hindrance, located in positions 4 and 5 of the oxazoline ring, were also experimented (Scheme 1).

In Cu(I)-catalyzed asymmetric cyclopropanation of styrene with ethyl diazoacetate in dichloromethane solution (Scheme 2) the crucial role played by matching−mismatching situations of axial and central stereogenic elements was emphasized. It was shown that the enantioselectivity was improved by the presence of electron-donor substituents on the biphenyl system. However, the differences in catalyst efficiency cannot be explained on the basis of pure electronic effects, since the variation of the substituents (R^1 in particular) on the biphenyl system produces a modification not only in the electronic properties but also in the steric features of the ligand by modifying the interanular torsion.

It is worth mentioning that a ligand of the above series (*S*,*S*,*S*-**1**, R^1 = Me, R^4 = *t*-Bu, R^2, R^3, R,[5] R^6 = H) had been previously employed to prepare sirenin in high enantiomeric purity level, through an intramolecular cyclopropanation reaction, in which traditional methylene bis(oxazoline) complexes behaved unsuccessfully.[2]

Other chiral atropisomeric ligands based on the same structural design, displaying a 1,1′-binaphthyl backbone, were found to give satisfactory results in asymmetric allylic oxidation[3] and in styrene cyclopropanation, provided that the diazoacetic ester would carry a very bulky (*tert*-butyl or menthyl) alcoholic moiety.[7]

More limited research was carried out in the series of ligands where the 2-(5-alkyl)oxazoline groups are bound to a conformationally flexible biaryl scaffold. The most representative work in this area refers to a study on the enantio- and diastereoselective cyclopropanation reaction of styrene with ethyl diazoacetate promoted by the Cu(I)−OTf complexes of ligands **1a**−**d** (R^1, R^2, R^3, R,[5] R^6 = H; **1a**, R^4 = *i*-Pr; **1b**, R^4 = *t*-Bu; **1c**, R^4 = Ph; **1d**, R^4 = CH_2Ph).[1] The best results reported were achieved with ligand **1b** (yield = 69%; *trans*/*cis* diastereomeric ratio 68/32; trans ee (%) = 74; *cis* ee (%) = 84).

Somewhat better data could be obtained with a selected enantiomer of menthyl diazoacetic ester, a strategy which masks the effective stereoselection ability of the ligand and involves further stereochemical information wasting (seven stereogenic elements in the reactants to produce two stereocenters in the products).

In the same study,[1] while two diastereoisomers were observed in solution for all the free ligands by ^{1}H NMR spectroscopy, in a ratio strongly dependent on solvent and temperature, with a calculated interconversion barrier of 15.5 kcal/mol at 10 °C in the case of **1b**, only one diastereoisomer was formed by complexation with copper(I) triflate− and palladium(II) dichloride−benzene complexes (calculations and NOE experiments suggested that it had identical axial and central stereogenicity descriptors). Two diastereomeric complexes were formed, however, when the metal was zinc(II) or silver(I).

The interpretation of this ample mass of results is, however, rather puzzling, and it is very difficult to draw clear indications on how to tune the steric and the electronic features of a bis(oxazoline) ligand to optimize the catalytic performances of its metal complexes in the copper(I) promoted stereoselective cyclopropanation of styrene with ethyl diazoacetate.

The aim of the present search was to investigate the effects exerted on stereoselectivity and reaction rate by the variation of electronic and steric parameters of the ligand, to give reliable indications for the design of new chiral catalytic mediators for this reaction.

The project was based on the synthesis of a series of electronically different chiral bis(oxazoline) ligands characterized by conformationally flexible or atropisomeric 3,3′-bithiophene backbone and their application in the

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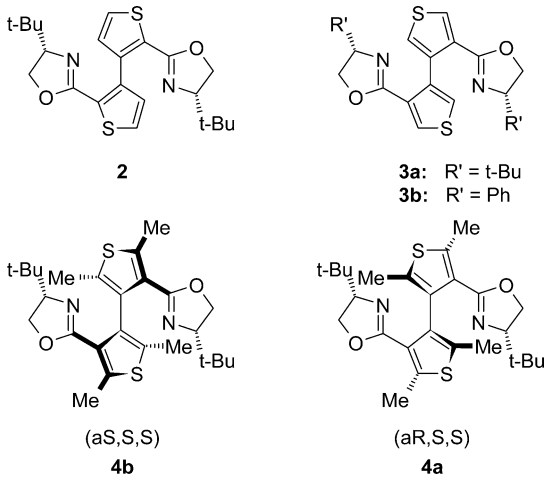
SCHEME 3. Electronically and Sterically Different Bis(oxazolines) with Conformationally Flexible or Atropisomeric 3,3′-Bithiophene Backbone



2 **3a:** R' = t-Bu **3b:** R' = Ph **4b** **4a**

Cu(I)-catalyzed stereoselective cyclopropanation of styrene with ethyl diazoacetate. (Scheme 3)

Bis(oxazoline) **1b** displaying the unsubstituted biphenyl scaffold was also resynthesized in order to directly compare the properties of the heteroaromatic ligands with those exhibited by the carbocyclic analogous.

Ligands **2** and **3a**, which are constitutional isomers, are expected to be quite similar in geometry, but the chelating functions in the former are more electron poor than in the latter, since the electronic density on the oxazoline imine moieties located in the position α to the thiophene ring suffer from the electron-withdrawing effect of the adjacent sulfur atom. Ligand **3b** was prepared in order to compare the effects produced on stereoselectivity by *tert*-butyl and phenyl groups. Rotation around the interanular bond in ligands **2** and **3a**,**b** should be completely free or, in any case, much less hindered than in the biphenyl analogous **1b**, given the different bond angles of five- and six-membered aromatic rings.

Ligands **4a** and **4b**, where rotation around the interanular bond is certainly precluded, are diastereoisomers differing in the configuration of the stereogenic axis. The electronic availability of the oxazoline rings is identical in both the isomers, which differ, instead, in their geometrical properties.

Results and Discussion

Synthesis of the Ligands. The synthesis of all of the ligands followed the same general strategy starting from the dicarboxylic acids **5a**−**c**, which were converted into the acid dichlorides **6a**−**c** and then into the diamides **7a**−**e** by reaction with L-(*S*)-*tert*-leucinol or (*S*)-phenylglycinol. All of the diamides were cyclized to bis(oxazolines) by reaction with the Burgess reagent[8] in tetrahydrofuran solution. As expected, two diastereomeric β-hydroxy diamides **7d** and **7e** were formed from acid dichloride **6c** and separated by column chromatography. The first eluted diamide **7d** was found to be the precursor of bis(oxazoline) **4b**, while **7e** afforded **4a** by reaction with the Burgess reagent. (Scheme 4)

As for the synthesis of starting dicarboxylic acids, their preparation was effected through different strategies. Acid **5a** was already cited in the literature[9] and was obtained in 74% yields by in situ carbon dioxide treatment of the 2,2′-dilithium derivative of 3,3′-bithiophene, directly prepared from the latter by reaction with 2 molar equiv of *n*-butyllithium in the presence of TMEDA. Better yields (88%) could be achieved by preparing the dilithium derivative starting from the 2,2′-dibromo-3,3′-bithiophene, obtained by bromination of the 3,3′-bithiophene with NBS in acetic acid−chloroform solution.

Analogously, the reaction of carbon dioxide with the 4,4′-dilithium derivative of 3,3′-bithiophene, synthesized by transmetalation of known 4,4′-dibromo-3,3′-bithiophene[10] with *n*-butyllithium, afforded acid **5b** in 71% yield.[11] The preparation of the 2,2′,5,5′-tetramethyl-3,3′-bithiophene-4,4′-dicarboxylic acid (**5c**) took advantage of the availability of 2,2′,5,5′-tetramethyl-4,4′-diiodo-3,3′-bithiophene.[12,13] Double lithiation of the latter with *tert*-butyllithium, followed by reaction with carbon dioxide, gave dicarboxylic acid **5c** in fairly good yields.[14]

Bis(oxazoline) **1b** was obtained according to the method reported in the literature.[1]

Electronic Properties of the Ligands. We considered the possibility of extending to the class of bis(oxazoline) ligands the electrochemical anodic peak potentials [$E_{p,a}$ (V)] as quantitative index of the electronic availability of the oxazoline nitrogen atom. We have found this parameter as highly representative of the electronic richness of the phosphorus function in many mono- and diphosphines.[13,15] The lower the $E_{p,a}$ value, the more electron rich the donor function of the ligand. In this light, we carried out voltammetric experiments on several bis(oxazolines) characterized by alkylidene and biarylidene scaffolds, under identical experimental conditions.

Commercially available methylene bis(oxazolines) **8a** and **8b** and the corresponding isopropylidene derivatives **8c** and **8d** were selected, since it has been documented that the mobility of the methylene hydrogens plays an important role in determining the mechanistic route of styrene cyclopropanation. (Scheme 5) We wondered whether the different behavior could be reflected in different electrochemical properties of the ligands.

In the series of biarylidene-based bis(oxazolines) we tested **1b**, displaying the biphenyl scaffold, and, in the series of biheteroaromatic ligands, diastereomeric **4a** and **4b** and conformationally unhindered **2** and **3b**. In the

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(11) Gronowitz, S. *Acta Chem. Scand.* **1961**, *15*, 1383.
(12) ,2′,5,5′-Tetramethyl-4,4′-diiodo-3,3′-bithiophene is the starting material employed to prepare the tetraMe-BITIOP, a chiral biheteroaromatic ligand,[13] currently produced by Chemi S.p.A. at a kiloscale level.
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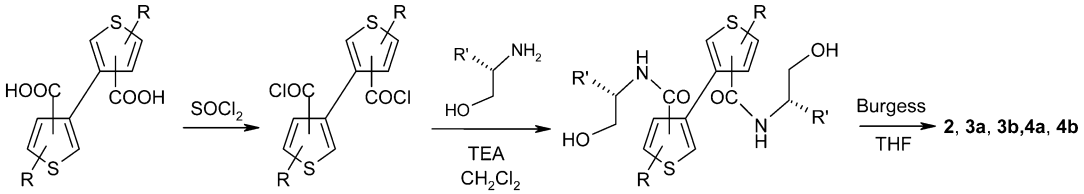
(15) Benincori, T.; Piccolo, O.; Rizzo, S.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 8340−8347.

SCHEME 4. Synthesis of Bis(oxazolines) with 3,3′-Bithiophene Backbone



5a
R = H
COOH in position 2

5b
R = H
COOH in position 4

5c
R = 2,5-diMe
COOH in position 4

6a
R = H
COCl in position 2

6b
R = H
COCl in position 4

6c
R = 2,5-diMe
COCl in position 4

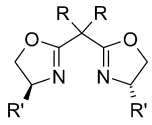
7a
R = H, R' = t-Bu
CO-N in position 2

7b
R = H, R' = t-Bu
CO-N in position 4

7c
R = H, R' = Ph
CO-N in position 4

7d, **7e**
R = 2,5-diMe, R' = t-Bu
CO-N in position 4

SCHEME 5. Methylene and Isopropylidene Bis(oxazolines) Submitted to Cyclovoltammetric Experiments



8

a	R = H	R' = Ph
b	R = H	R' = *t*-Bu
c	R = Me	R' = Ph
d	R = Me	R' = *t*-Bu

latter series, we had to take into account that also the bithiophene moiety was expected to undergo electrochemical oxidation, giving rise to a wave which should have been necessarily distinguished from that produced by the oxazoline ring.

The data obtained from cyclovoltammetric experiments, carried out under identical experimental conditions, are reported in Table 1, while the curves obtained in the case of diastereoisomers **4a** and **4b** are reported in Figure 1 as examples of the electrochemical behavior of these compounds.

Examination of the CV data suggest somes interesting observations. The oxidative peak potential of methylene bis(oxazolines) **8a** and **8b** is significantly lower than that displayed by the corresponding *iso*-propylidene derivatives, **8c** and **8b**, suggesting a higher hyperconjugative electronic density of the nitrogen atom in the unsubstituted ligands

This observation is in agreement with the hypothesis that the mobility of the methylene protons would play an important role in the phenomena involving nitrogen complexation.

Phenyl and *tert*-butyl groups have nearly identical influence on the electronic properties of the adjacent imine function of the oxazoline ring.

All of the ligands displaying the 3,3′-bithiophene backbone show a first anodic peak in a range (1.3−1.7 V) which is typical for bithiophene substrate oxidation[16] and a second peak at quite higher potentials which should correspond to the oxazoline nitrogen oxidation. Assignation of the peaks occurring at lower potentials to the oxidation of the bithiophene moiety is supported by the CV experiments carried out on the biphenyl-based bis(oxazoline) ligand **1c** and on the amide **7d**, precursor of ligand **4b**. The peak at lower potential is absent in the former case, while it reappeared at 1.51 V in the latter, followed by a second peak at 1.96 V, in line with the anodic peak values known for secondary amides oxidation.[17]

Of course, in the cases of the bis(oxazolines) with a bithiophene scaffold, featuring two subsequent oxidation peaks, it is possible that the first electron abstraction may influence the second oxidation step, which could hinder a reliable, systematic comparison of the CV data along the whole series of ligands. However, the experimental peak potentials for the second oxidation step of **2**, **3b**, **4a**, and **4b** (1.66−1.87 V) are very close to those found for the other bis(oxazolines) devoid of the bithiophene scaffolds (1.79−2.03 V), thus pointing to two independent, or nearly independent, anodic oxidation steps.

In the bithiophene series, the oxazoline system of **2**, located in position α of the thiophene ring, exhibits a more electron-poor nitrogen atom than **3**, **4a,** and **4b**, where the oxazoline ring is bound to the β position, as discussed before. The electron-releasing effect of the two methyl groups present on each thiophene ring is in agreement with the reduced $E_{p,a}$ value found for **4a** and **4b**. It is also expected that diastereoisomers **4a** and **4b** would display different anodic peak potentials.

It is worth noting that **1b** is the most electron poor of the biaromatic ligands, in accordance with the consideration that biphenyl is a more electron-poor system than 3,3′-bithiophene.

Stereochemical Features of the Ligands. ^{1}H NMR spectroscopy analysis clearly demonstrated that rotation around the 3,3′-bithiophene interanular bond was completely free in bis(oxazoline) ligands **2** and **3a,b**, while, as anticipated, two diastereoisomers were observed in solution for ligand **1b**.[1]

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TABLE 1. Electrochemical Anodic Peak Potentials vs SCE of Bis(oxazolines)

ligand	**8a**	**8b**	**8c**	**8d**	**1b**	**2**	**3b**	**4a**	**4b**
$E_{p,a}$[a] (V)	1.80	1.79	1.96	2.03	1.99	1.92 (1.62)	1.87 (1.45)	1.66 (1.29)	1.82 (1.33)

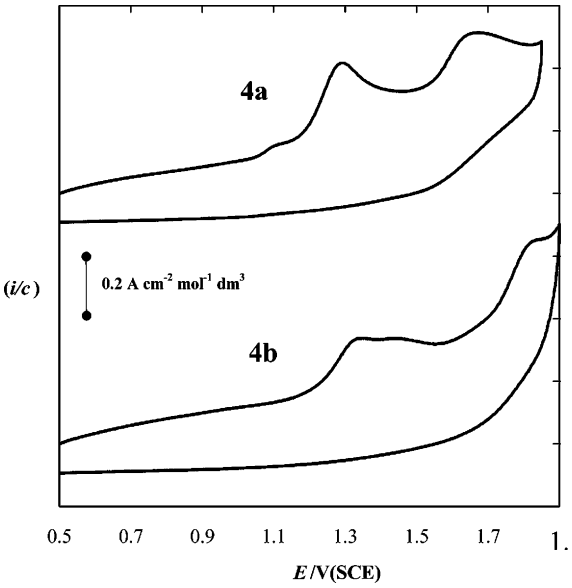

FIGURE 1. Cyclovoltammetric characteristics of **4a** and **4b** (anodic peaks). Key: solvent, acetonitrile; supporting electrolyte, tetrabutylammonium perchlorate; substrate concentration, 10^{-3} M; scan rate, 0.2 V s^{-1}; working electrode, glassy carbon; counter-electrode, Pt wire; reference electrode, SCE [$E_{Fc+|Fc}$ = 0.393 V (SCE) in the working medium].

All of the ligands underwent total complexation by reaction with equimolar amounts of Cu(I)OTf(C_6H_6) (or [Cu(I)PF_6(C_6H_6)]) in $CDCl_3$ solution, as clearly indicated by the strong chemical shift variation of most of the signals of the free ligand observed after the addition of copper(I). The spectra of the complexes resulting from **4a** and **4b** could be analyzed in detail, since all of the signals were sharp and perfectly legible. In the case of bis(oxazoline) **2** and **3b**, chemical shift variation following complexation was accompanied by extensive signal broadening, indicating the presence of several species in stereodynamic equilibrium in solution. An intermediate situation was found in the case of ligands **3a**, where some broadening of the signals, suggesting again the presence of several species in solution, did not preclude the individuation of a major species.

A few selected ^{1}H NMR data of free and complexed ligands **3a**, **4a**, and **4b** are summarized in Table 2.

The unquestionable proof of the configuration of the stereogenic axis in diastereomeric bis(oxazoline) ligands **4a** and **4b** was given by X-ray diffraction analysis performed on a crystal of **4a**, where absolute configuration was found to be R. The Cu(I) complex of **4a** should correspond, by consequence, to the catalytically less active Cu(I) complex of **1b**,[1] as also expected on the basis of molecular modeling analysis[18](Figure 2).

(18) The energy minima for bis(oxazolines) **4a** and **4b** were calculated by using the Macromodel 5.5 program and the MM* computing method. Then, bond lengths and angles were calculated for the most stable conformations, which were found to be the most suitable to copper chelation.

Cu(I)-Catalyzed Asymmetric Cyclopropanation of Styrene. In a typical experimental procedure, freshly distilled styrene (1 mmol) was added to the chiral catalyst, prepared by stirring the chiral ligand (5, 25, or 50 μm) and equimolar amounts of commercially available CuOTf·0.5PhH in dry CH_2Cl_2 under nitrogen at rt for 0.5 h. A solution of ethyl diazoacetate (0.5 mmol) in CH_2Cl_2 was added by a syringe pump over a period of 14 h, and the reaction was stirred for a further 10 h at rt. The mixture was then concentrated under vacuum, and the residue, dissolved in CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude product that was purified by flash chromatography with a 95:5 hexane/AcOEt mixture as eluant. Yields, trans/cis stereoselectivity, and ee of reaction products are reported in Table 3.

The data reported above deserve a few comments.

The discrepancy between the data obtained by us and those reported in the literature for the reaction promoted by the Cu(I) complex of **1b** (entries 1 and 2) might be explained on the basis of some differences in the experimental procedure, like the different ratio of the two reagents. In particular, ethyl diazoacetate was the stoichiometrically limiting reagent in our experiments, while styrene was the limiting reagent in the literature procedure (1/1.3 styrene/ethyl diazoacetate molar ratio).[1,20] In agreement with this hypothesis, even though other factors might influence the reaction rate, kinetic studies have shown that olefin excess may slow the cyclopropanation rate, due to the existence of a preequilibrium involving the formation of the catalyst−olefin complex and clearly depending on the nature of the ligand.[21] In this context, it is more appropriate to consider entry 1 for comparative purposes.

The analogy of the results obtained with the axially blocked bithiophene ligand with matching stereochemistry **4b** (entry 7) and with the biphenyl-based bis(oxazoline) **1b** (entry 1) is striking in all respects: yields and diastereo- and enantioselectivity.

Given the considerable difference in the electronic availability of the two ligands, we are led to believe that this parameter does not play a crucial role in styrene cyclopropanation. Instead, much more important seems to be the geometry of the ligand, which must be fixed or, at least, variable within quite narrow limits.

In agreement with this assumption is the observation that the axially free bis(oxazolines) **2** and **3a**,**b** (entries 3−5) lead to nearly racemic products. With these ligands not only both of the possible diastereomeric Cu(I) com-

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(20) To further validate the results obtained in the cyclopropanation reaction, the procedure was repeated by employing copper(II) trifluoromerhanesulfonate/bis-oxazoline **4b** complex that was reduced in situ by adding phenylhydrazine. Similar results, in terms of yield and enantioselectivity, were obtained.

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TABLE 2. ^{1}H NMR($CDCl_3$) Chemical Shifts of 3, 4a, 4b, and Their Cu(I)−OTf Complexes

3a	**3a**−Cu(I)OTf[a]	**4a**	**4a**−Cu(I)OTf	**4b**	**4b**−Cu(I)OTf[b]
7.88 (d) 1H	7.90 (d) 1H	3.80−3.98 (m) 3H	4.40−4.50 (m) 2H, 4.17 (dd) 1H (J = 6 Hz, 12 Hz)	4.01 (m) 1H	4.54 (m) 2H
7.20 (d) 1H	7.15 (d) 1H			3.82 (m) 2H	4.08 (m) 1H
4.05−3.75 (m) 3H	4.50−4.40 (m) 2H, 4.30−4.12 (m) 1H	2.60 (s) 3H	2.48 (s) 3H		
		2.04 (s) 3H	1.94 (s) 3H	2.54 (s) 3H	2.47 (s) 3H
				2.14 (s) 3H	2.03 (s) 3H
0.77 (s) 9H	0.71 (s) 9H	0.81 (s) 9H	0.73 (s) 9H	0.76 (s) 9H	0.98 (s) 9H

[a] The data reported in the table refer to the signals of the main species present in solution. Some other broad signals are present at fields typical of aromatic and *t*-Bu protons. [b] Similar data were exhibited by the analogous Cu(I)PF_6 complex: 4.64 (t) 1H (J = 12 Hz), 4.54 (t) 1H (J = 12 Hz), 3.98 (t) 1H (J = 12 Hz), 2.46 (s) 3H, 2.03 (s) 3H, 0.98 (s) 9H.

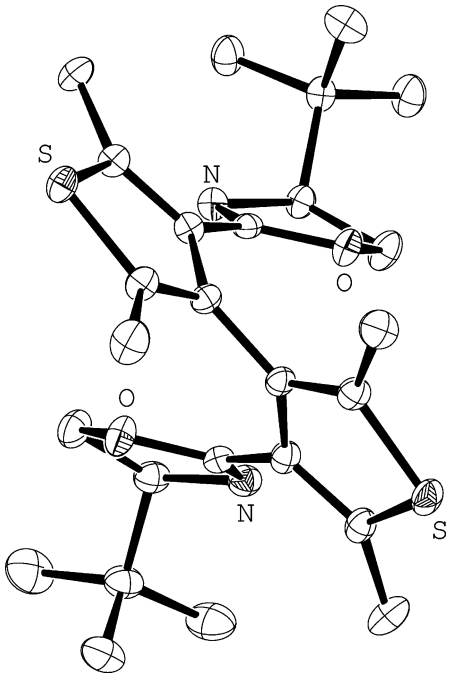

FIGURE 2. ORTEP presentation of diastereoisomer **4a** at 150 K, projected along the non crystallographic C_2 axis. Hydrogen atoms are omitted for clarity.

TABLE 3. Cu(I)-Catalyzed Asymmetric Cyclopropanation of Styrene

					trans	
entry	ligand	substrate/ catalyst[a]	yield[b] (%)	trans/cis[c]	ee[d] (%)	abs config[e]
1	**1b**	100	29	77/23	65	1*R*,2*R*
2	**1b**[f]	100	69	68/32	74	1*R*,2*R*
3	**2**	100	30	57/43	2	1*S*,2*S*
4	**3a**	100	29	75/25	6	1*R*,2*R*
5	**3b**	100	32	70/30	11	1*R*,2*R*
6	**4a**	100	12	73/27	16	1*R*,2*R*
7	**4b**	100	30	74/26	67[g]	1*R*,2*R*
8	**4b**	20	55	67/33	66	1*R*,2*R*
9	**4b**	10	81	67/33	67[h]	1*R*,2*R*

[a] Ethyl diazoacetate/Cu(I) molar ratio. [b] Isolated yield of the mixture of *trans*- and *cis*-diastereoisomers. [c] Determined by ^{1}H NMR and HPLC. [d] Determined by HPLC on chiral stationary phase. [e] Determined by comparison of the $[\alpha]_D$ sign with the data reported in the literature.[19] [f] Literature data.[1] [g] ee (%) *cis* = 52. [h] ee (%) *cis* = 48.

plexes are formed, but also the complexes themselves are not rigid enough to display a reasonable facial recognition ability. The strong influence on the enantiomeric excesses of the geometry of the chelating core (five-, six-, or seven-membered chelate ring) and of the bite angle of the complex in the stereoselective cyclopropanation of styrene is well documented.[19,22]

It is worth noting that the Cu(I) complex of ligand **4a**, where axial and central descriptors are different, which probably displays a rigid but unfavorable spatial architecture, produces very modest results not only in the stereselection levels but also in catalytic activity (entry 6). The latter observation is a further demonstration of the overwhelming importance of steric effects on electronic factors in this reaction.

Some further experiments were devoted to checking the effects of lower molar substrate/catalyst ratios on conversion and enantioselectivity (entries 8 and 9). We found that a progressive decrease in the S/C ratio was followed by a parallel increase in the conversion levels, checked at the same reaction time, as expected, even though the TOF value was also substantially lowered.

Conclusions

The results of this research give some basic instruction for designing new bis(oxazolines) to be employed as ligands of Cu(I) in the stereoselective cyclopropanation of styrene with ethyl diazoacetate.

Steric properties of the ligand seem to play a crucial role in controlling both the stereoselection levels and the reaction rate: the suggestion is that the scaffold bearing the chelating functions would be rigid and capable of orienting the oxazoline moieties in such a way as to direct the 4-position substituents in a quasi-anti arrangement around the metal core of the complex.

The second suggestion concerns the electronic properties of the biaryl-based ligands studied in this work, which seem to be scarcely relevant in this specific reaction. This is a quite interesting result, since the electronic availability of the metal chelating function is, instead, an extremely critical point in other types of reactions, like the hydrogenation of carbon−oxygen- and carbon−carbon-functionalized double bonds[13] and the Diels−Alder cycloaddition reactions,[23] where the electronic richness of the ligand can enhance the reaction

(22) For a recent discussion on the influence of the substitution pattern at the box bridging carbon on the steric course of a box-mediated asymmetric synthesis, see: Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878 and references therein. For a study on the importance of byte angle in bis(oxazoline) systems, see also: Davies, I. W.; Deeth, R.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 1233−1236.

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rate of some powers of ten. An opposite, but equally relevant, effect was found in some palladium-mediated carbon−carbon bond-forming reactions, where medium-rich diphosphines appear to give much more active complexes than the electron-rich ones.[24]

Even though the comparison of the catalytic performances of the complexes of structurally different ligands is questionable, it is worth comparing the behavior of the biaryl-based with Evans-type bis(oxazolines). It is interesting to note how ligands endowed with similar electronic properties display completely different catalytic activities, further suggesting that the electronic properties do not play a decisive role.

Recent theoretical studies[25] have demonstrated that the copper(I)-mediated cyclopropanation proceeds via a metal−carbene complex, formed by association of the diazo compound to the catalyst with concomitant extrusion of nitrogen. The formation of the copper−carbene intermediate is the rate-determining step,[26] while the direct carbene insertion into the double bond, which leads to the different isomeric cyclopropanes and which is responsible of the stereochemical outcome of the reaction, occurs after this step. Although special care must be taken in order to compare theoretical studies with real cases,[27] it is worth mentioning that density functional theory (DFT) calculations have shown that steric interactions between the ester group of the diazo compound and substituents on the bis(oxazoline) and the geometry of chelate ligand−Cu complex are responsible for the enantio- and diastereoselectivity of the process.[28] These recent findings support the results of the present research, where steric factors and catalyst geometrical features clearly overwhelm any consideration of the electronic properties of the chiral ligands.[29]

In this work, the electrochemical oxidative potential was employed for the first time the as a tool to quantitatively evaluate the electronic availability of the nitrogen function in oxazolines, a parameter which was found to be very useful and reliable in the case of phosphorus ligands.

Experimental Section

General Procedure for the Synthesis of the Dicarboxamides 7a−e. A solution of the dicarboxylic acid dichloride (1 mmol) in dry CH_2Cl_2 was dropped, under nitrogen, at 0 °C into a stirred solution of TEA (2 mmol) and (*S*)-*tert*-leucinol or (*S*)-phenylglycinol (2 mmol) in dry CH_2Cl_2. The reaction mixture was stirred at rt for 1 night and then washed with 1 N HCl and then with water. The organic layer was separated and dried (Na_2SO_4) and the solvent removed under reduced pressure to afford crude compounds **7a**−**e** which were purified by crystallization or chromatography.

2,2′-Bis[*N*-(1′*S*)-(1′-*tert*-butyl-2′-hydroxyethyl)carboxamido]-3,3′-bithiophene (7a): yield 90%; mp 206 °C (toluene); ^{1}H NMR δ 7.67 (d, 2H, J = 3.77 Hz), 7.09 (d, 2H, J = 3.77 Hz), 5.97 and 5.95 (broad d, 2 NH), 3.88 (m, 2H), 3.75 (dd, 2H, J_1 = 11.5 Hz and J_2 = 3.42 Hz), 3.32 (dd, 2H, J_1 = 11.5 Hz and J_2 = 7.34 Hz), 2.52 (broad s, 2H), 0.71 (s, 18H); ^{13}C NMR 27.0, 33.7, 59.9, 62.6, 130.5, 131.4, 134.3, 138.7, 162.0; MW 452.63 Da. Anal. Calcd for $C_{22}H_{32}N_2O_4S_2$: C, 58.38; H, 7.13; N, 6.19. Found: C, 58.10; H, 7.11; N, 6.35.

4,4′-Bis[*N*-(1′*S*)-(1′-*tert*-butyl-2′-hydroxyethyl)carboxamido]-3,3′-bithiophene (7b): yield 70%; mp 145 °C (triturated with diethyl ether); ^{1}H NMR δ 8.26 (d, 2H, J = 3.5 Hz), 7.44 (d, 2H, J = 3.5 Hz), 5.75 and 5.77 (broad d, 2H), 3.85 (m, 2H), 3.74 (dd, 2H, J_1 = 11.7 Hz and J_2 = 3.07 Hz), 3.32 (dd, 2H, J_1 = 11.7 Hz and J_2 = 6.56 Hz), 2.52 (broad s, 2 H), 0.75 (s, 18H); ^{13}C NMR 26.0, 32.8, 60.9, 66.6, 131.5, 132.4, 135.3, 140.0, 162.0; MW 452.63 Da. Anal. Calcd for $C_{22}H_{32}N_2O_4S_2$: C, 58.38; H, 7.13; N, 6.19. Found: C, 58.20; H, 7.21; N, 6.25.

4,4′-Bis[*N*-(1′*S*)-(1′-phenyl-2′-hydroxyethyl)carboxamido]-3,3′-bithiophene (7c): yield 76%; mp 135−138 °C (triturated with diethyl ether); ^{1}H NMR δ 8.15 (d, 2H, J = 3.44 Hz), 7.39 (d, 2H, J = 3.44 Hz), 7.25 (m, 6H), 7.04 (m, 4H), 6.36 and 6.33 (broad d, 2H), 5.07 (m, 2H), 3.89 (dd, 2H, J_1 = 11.66 Hz and J_2 = 3.51 Hz), 3.64 (dd, 2H, J_1 = 11.66 Hz and J_2 = 5.65 Hz), 3.25 (broad s, 2H), 0.75 (s, 18H); MW 492.61 Da. Anal. Calcd for $C_{26}H_{24}N_2O_4S_2$: C, 63.39; H, 4.91; N, 5.69. Found: C, 63.19; H, 4.88; N, 5.72.

2,2′,5,5′-Tetramethyl-4,4′-bis[*N*-(1′*S*)-(1′-*tert*-butyl-2′-hydroxyethyl)carboxamido]-3,3′-bithiophene (7d) and (7e). Column chromatography (SiO_2, eluant hexane/AcOEt 1:1). The first product eluted was **7d**: yield 32%; mp 219 °C; $[\alpha]^{25}_D$ = −26 (c = 1, $CHCl_3$); ^{1}H NMR δ 6.75 and 6.72 (broad d, 2H), 3.82 (m, 2H), 3.72 (dd, 2H, J_1 = 11.2 Hz and J_2 = 3.33 Hz), 3.57 (dd, 2H, J_1 = 11.2 Hz and J_2 = 8.12 Hz), 2.52 (s, 6H), 2.12 (s, 6H), 1.95 (broad s, 2H), 0.87 (s, 18H); ^{13}C NMR 13.7, 14.6, 27.3, 33.7, 60.1, 63.6, 131.5, 134.9, 135.6, 137.2, 167.8; MW 508.71 Da. Anal. Calcd for $C_{26}H_{40}N_2O_4S_2$: C, 61.38; H, 7.93; N, 5.51. Found: C, 61.10; H, 7.81; N, 5.35.

The second product eluted was **7e**: yield 32%; mp 195 °C; $[\alpha]^{25}_D$ = −8 (c = 0.54, $CHCl_3$); ^{1}H NMR δ 6.00 (broad s, 2H), 3.82 (m, 2H), 3.73 (dd, 2H, J_1 = 11.7 Hz and J_2 = 3.06 Hz), 3.57 (dd, 2H, J_1 = 11.7 Hz and J_2 = 6.52 Hz), 2.65 (s, 6H), 2.25 (broad s, 2H), 2.20 (s, 6H), 0.87 (s, 18H); ^{13}C NMR 13.3, 15.2, 26.7, 33.4, 59.3, 62.4, 130.7, 132.4, 134.0, 142.4, 165.4; MW 508.71 Da. Anal. Calcd for $C_{26}H_{40}N_2O_4S_2$: C, 61.38; H, 7.93; N, 5.51. Found: C, 61.20; H, 7.83; N, 5.55.

General Procedure for the Synthesis of the Bisoxazolines 2, 3a, 3b, 4a, and 4b. The Burgess reagent (methyl *N*-{[(triethylammonio)sulfonyl]carbamate) (2 mmol) was added to a solution of the dicarboxamide (1 mmol) in THF. The reaction mixture was stirred for 24−72 h. The white precipitate was filtered off and the residue filtered over SiO_2 pad to give the bisoxazoline derivative in a pure state.

2,2′-Bis[(*S*)-4,5-dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]-3,3′-bithiophene (2): reaction time 72 h; filtered over a SiO_2 pad with CH_2Cl_2/AcOEt 9:1 as eluant; yield 80%; ^{1}H NMR δ 7.33 (d, 2H, J = 5.11 Hz), 7.02 (d, 2H, J = 5.11 Hz), 4.07 (m, 4H), 3.87 (dd, 2H, J_1 = 10.2 Hz and J_2 = 6.9 Hz); ^{13}C NMR 26.2, 34.4, 69.4, 77.1, 127.0, 131.5, 131.1, 138.6, 159.4; MW 416.60 Da. Anal. Calcd for $C_{22}H_{28}N_2O_2S_2$: C, 63.43; H, 6.77; N, 6.72. Found: C, 63.90; H, 6.81; N, 6.75.

4,4′-Bis[(*S*)-4,5-dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]-3,3′-bithiophene (3a): reaction time 24 h; filtered over SiO_2 pad with CH_2Cl_2/AcOEt 9:1 as eluant; yield 80%; ^{1}H NMR δ 7.87 (d, 2H, J = 3.39 Hz), 7.18 (d, 2H, J = 3.39 Hz), 4.07 (dd, 2H, J_1 = 9.9 Hz and J_2 = 8.1 Hz), 3.86 (m, 4H); ^{13}C NMR 26.6, 36.5, 67.1, 75.1, 127.6, 130.0, 131.9, 139.0, 161.1; MW 416.60 Da. Anal. Calcd for $C_{22}H_{28}N_2O_2S_2$: C, 63.43; H, 6.77; N, 6.72. Found: C, 68.10; H, 6.71; N, 6.55.

4,4′-Bis[(*S*)-4,5-dihydro-4-(phenyl)oxazol-2-yl]-3,3′-bithiophene (3b): reaction time 24 h; filtered over SiO_2 pad with hexane/AcOEt 8:2 as eluant; yield 80%; $[\alpha]^{25}_D$ = −3.6 (c = 1, $CHCl_3$); mp 122 °C; ^{1}H NMR δ 8.04 (d, 2H, J = 3.4 Hz), 7.21 (m, 12H), 5.18 (dd, 2H, J_1 = 9.8 Hz and J_2 = 8.77 Hz),

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4.51(dd, 2H, J_1 = 10 Hz and J_2 = 8.33 Hz), 3.95 (t, 2H, J = 8.33 Hz); ^{13}C NMR 70.0, 74.3, 125.4, 126.9, 127.6, 128.8, 130.0, 137.2, 142.9, 161.4; MW 456.58 Da. Anal. Calcd for $C_{26}H_{20}N_2O_2S_2$: C, 68.40; H, 4.41; N, 6.13. Found: C, 68.10; H, 4.71; N, 6.35.

(*S*)-2,2′,5,5′-Tetramethyl-4,4′-bis[(*S*)-4,5-dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]-3,3-bi-thiophene (4b): Starting material, **7d**; reaction time, 24 h; filtered over SiO_2 pad with hexane/AcOEt 8:2 as eluant: yield 80%; $[\alpha]^{25}_D = -45.6$ (c = 1, $CHCl_3$); ^{1}H NMR δ 3.91 (m, 6H), 2.62 (s, 6H), 2.07 (s, 6H), 0.83 (s, 18H); ^{13}C NMR 13.2, 25.6, 33.5, 67.7, 76.5, 126.7, 133.2, 133.5, 138.5, 160.5; MW 472.71 Da. Anal. Calcd for $C_{26}H_{36}N_2O_2S_2$: C, 66.06; H; 7.68; N, 5.93. Found: C, 66.10; H, 7.71; N, 6.05.

(*R*)-2,2′,5,5′-Tetramethyl-4,4′-bis[(*S*)-4,5-dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]-3,3-bithiophene (4a): starting material, **7e**. reaction time, 24 h; filtered over SiO_2 pad with hexane/AcOEt 8:2 as eluant; yield 80%; Oil which solidified on standing; mp 67 °C; $[\alpha]^{25}_D = -81$ (c = 1, $CHCl_3$); ^{1}H NMR δ 4.02 (m, 2H), 3.83 (m, 4H), 2.56 (s, 6H), 2.15 (s, 6H), 0.78 (s, 18H); ^{13}C NMR 14.2, 15.5, 26.3, 34.1, 68.4, 76.6, 127.2, 133.6, 133.9, 138.9, 161.0; MW 472.71 Da. Anal. Calcd for $C_{26}H_{36}N_2O_2S_2$: C, 66.06; H, 7.68; N, 5.93. Found: C, 66.20; H, 7.61; N, 6.07.

General Procedure for the Cyclopropanation Reaction. A solution of the catalyst was prepared by stirring, at rt for 0.5 h under nitrogen, the bisoxazoline (0.1 mmol) and commercially available CuOTf·0.5PhH (0.09 mmol) in dry CH_2Cl_2 (6 mL). Freshly distilled styrene (5 mmol) was added to the resulting bright green solution. Ethyl diazoacetate (0.9 mmol) dissolved in CH_2Cl_2 (3 mL) was added over a period of 14 h by a syringe pump, and the reaction was stirred for 20 h at rt. The mixture was then concentrated under vacuum and the residue flash chromatographed with a 95:5 hexane/diethyl ether mixture as eluant to isolate the *cis* and *trans* diastereoisomers.

Stereoselectivity Evaluation. Diastereoselectivity evaluation (*trans*/*cis* ratio) was performed by ^{1}H NMR spectroscopy and HPLC analysis. Enantiomeric excesses were determined by HPLC on chiral stationary phase.

Trans isomer: column, Chiracel OD; eluant, *n*-hexane/*i*-PrOH 95:5; flow rate, 1 mL/min; UV detector, 230 nm; retention time of (*R*,*R*)-isomer, 5.15 min; retention time of (*S*,*S*)-isomer: 5.90 min. Cis isomer: column, Chiracel OB; eluant, *n*-hexane/*i*-PrOH 99:1; flow rate, 1 mL/min; UV detector, 230 nm; retention time of (*S*,*R*)-isomer, 29.0 min; retention time of (*R*,*S*)-isomer, 26.3 min.

X-ray Structure Determination of 4a.[30] Crystal data: $C_{26}H_{36}N_2O_2S_2$, FW = 472.69, colorless crystal 0.46 × 0.32 × 0.08 mm^3, monoclinic, space group $P2_1$, a = 9.4604(15) Å, b = 9.2409(15) Å, c = 14.710(2) Å, β = 95.02(2)°, V = 1281.1(3) Å^3, Z = 2, ρ_{calc} = 1.225 g cm^{-3}, radiation Mo Kα (λ = 0.71073 Å), μ(Mo Kα) = 0.233 mm^{-1}, 19083 reflections measured at 150 K (Bruker APEX CCD diffractometer, equipped with an OXFORD low-temperature device) below θ = 29.04 °; 6783 unique reflections [6616 with $I > 2\sigma(I)$], R_{avg} = 0.0320. The structure was solved by SIR2002[31] and refined on F^2 using SHELXL;[32] 433 parameters refined, final indices R(all) = 0.0476, wR = 0.1104, goodness-of-fit 1.190, map residues from −0.30 to +0.47 eÅ^{-3}.

Electrochemical Experiments. The CV characteristics were recorded at scan rates ranging from 0.02 to 20 V s^{-1}, and with ohmic drop compensation (by the positive feedback technique). The working solutions, carefully deareated by nitrogen bubbling, were made up by HPLC-grade acetonitrile ACN with 0.1 M tetrabutylammonium perchlorate TBAP (>99%) as the supporting electrolyte, the substrate concentrations ranging from 0.0004 to 0.001 mol dm^{-3}. The working cell included a glassy carbon GC disk (surface = 0.071 cm^2), polished with diamond powder (diameter 1 μm) on a wet cloth, as the working electrode; a Pt wire as the counter electrode; and an aqueous saturated calomel electrode (SCE) as the working reference electrode. To refer the experimental peak potentials to the ferricinium/ferrocene (Fc^+|Fc) reference redox couple, according to the IUPAC criterion[33] the half-wave potential $E_{1/2} = (E_{p,c} + E_{p,a})$ of ferrocene was measured on GC electrode in our working medium, yielding $E_{1/2}$ = 0.393 V (SCE)).

Acknowledgment. We thank Dr. Matteo Zacchè (Laboratori Alchemia s.r.l., Milan, Italy) for computational work and Dr. Alessandro Viano (INSTM-Wiz Chemicals, Firenze, Italy) for enthusiastic cooperation in the development of the experimental work. Dr. T. Benincori thanks the Dipartimento di Chimica Organica e Industriale of the University of Milan for hospitality.

Supporting Information Available: X-ray diffraction data of **4a** including tables of positional and isotropic thermal parameters, anisotropic thermal parameters, interatomic bond distances, intramolecolar and torsion angles. Synopsis of CV characteristics for the tested compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050267M

(29) For an example where other factors, like hydrogen bond, were shown to play an important role in determining the stereochemical outcome of the reaction, see: Suenobu, K.; Itagaki, M.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 7271−7280.

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