Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2311–2316

TETRAHEDRON: *ASYMMETRY*

Electrochemically-initiated Michael addition of chiral acetoacetic derivatives to methyl vinyl ketone: stereocontrolled construction of quaternary carbon centers

Laura Palombi,[a,*] Marta Feroci,[b] Monica Orsini[a] and Achille Inesi[a,*]

[a]*Dip. di Chimica, Ingegneria Chimica e Materiali, 67040-Monteluco di Roio, L'Aquila, Italy*
[b]*Dip. di Ingegneria Chimica, Materiali, Materie Prime e Metallurgia, Via Castro Laurenziano 7, I-00161 Roma, Italy*

Received 3 August 2002; accepted 25 September 2002

Abstract—Stereoselective conjugate addition of chiral β-dicarbonyl derivatives to methyl vinyl ketone was promoted by electrolysis, using a catalytic amount of electricity. With respect to the metal-catalyzed methods, the electrochemical, metal-free conditions resulted in enhanced reactivity of the electrogenerated enolates, so that the Michael addition was found to occur under mild conditions and short reaction times, affording products with significant diastereoisomeric excesses. When Oppolzer's sultam was used as the chiral inductor and prolonged reaction times were employed, a reversal in the stereoselectivity was observed, evidencing kinetic control in the electrochemically-induced addition and subsequent thermodynamic equilibration. The electrochemically-based method was also exploited for the elaboration of quaternary stereogenic carbon centers.

1. Introduction

Asymmetric conjugate addition of active methylene compounds to activated unsaturated systems (asymmetric version of the Michael reaction) represents a powerful and widespread tool for stereoselective C–C bond formation.

Because of several well-known drawbacks related to the traditional base-catalyzed procedures,[1] many efforts have been made to establish valuable synthetic alternatives. Most of the methods available[2] involve the use of metal catalysts associated with chiral auxiliaries. Indeed, many different transition metal species and enantiomerically pure ligands have been proposed in order to improve the chemo- and stereoselectivity of the addition processes.[3]

On the other hand, a significantly different approach to achieve this goal consists of the insertion of a chiral inductor in the acceptor or in the donor molecule to stereodifferentiate the nucleophilic attack.[4,5]

In this case, also following a poorly stereoselective addition process, the newly created stereogenic center can often be obtained in enantiomerically pure form by resolution of the epimeric mixture through a number of different techniques.

In a recent report by Moreno-Mañas,[5] for instance, the presence of an enantiopure 4-benzyl-oxazolidin-2-one residue on the acetoacetic skeleton was exploited for diastereoselective additions to various Michael acceptors, by means of a catalytic Ni(II) complex. Using alkyl vinyl ketones as electrophiles, the obtained epimeric mixtures were found to be configurationally stable, and separation by column chromatography was readily accomplished.

However, although the Ni(II)-mediated addition allows the reactions to occur under neutral conditions and with high chemoselectivity, complete conversion of the starting material may require long reaction times (1–5 days) and/or moderate heating (50°C refluxing 1,2-dichloroethane), as a result, epimerization due to the presence of an enolizable proton has occasionally been observed.

As is well known, various Michael reactions are effectively catalyzed by electrogenerated bases[6] or by direct cathodic electrolysis.[7] As an interesting application,

* Corresponding authors. Tel.: +39-0862-434248; fax: +39-0862-434203 (L.P.); tel.: +39-0862-434216; fax: +39-0862-434203 (A.I.); e-mail: palombi@ing.univaq.it; inesi@ing.univaq.it

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00636-5

Evans reported the diastereoselective conjugate addition to levoglucosenone by direct reduction to the electrode (using thiols as nucleophiles) or via electrogenerated superoxides (using nitro or heterocyclic compounds as nucleophiles).[8]

As part of our research program directed towards developing new electrochemically-based synthetic procedures,[9] we became interested in designing asymmetric bond-forming reactions by electrochemical activation of chiral substrates, under metal-free conditions.

In this context, by means of electrochemical generation of nitrogen and carbon anions, our laboratory has successfully achieved synthetic targets both in the diastereoselective conjugate additions of chiral nitrogen nucleophiles,[10] and in diastereoselective alkylation of chiral β-dicarbonyl compounds.[11]

It should be noted that, in both cases, owing to the lack of any metal counterion, we noticed a marked reactivity of the electrogenerated anions, so that the reactions were found to proceed with short reaction times, under mild conditions, avoiding the use of chemical bases, metallic reagents or additives (such as crown ethers etc.) to increase the reactivity.

We report herein our studies on the reactivity and stereoselectivity of different β-dicarbonyl enolates incorporating chiral auxiliaries as donors in the Michael addition reaction with methyl vinyl ketone (MVK), under electrochemical conditions.

2. Results and discussion

2.1. Electrochemically-promoted addition of *N*-acetoacetyl oxazolidin-2-one

We have already reported on a previous study,[11] which showed that electrochemical deprotonation of *N*-acetoacetyl oxazolidin-2-ones can be very efficiently performed by electrolysis, under galvanostatic control, of acetonitrile/tetraethylammonium perchlorate (TEAP) solutions containing the active methylene compound. The corresponding tetraethylammonium enolates were obtained in nearly quantitative yield after consumption of 1.2 F/mol current, and used for efficient alkylations with organohalides.

In connection with the above investigations, we tested the reactivity of **1a**[12] (chosen as a model compound) in the conjugate addition to the representative Michael acceptor MVK under a variety of experimental conditions (Scheme 1).

As shown in Tables 1 and 2, to find the optimal electrochemical conditions, two sets of experiments concerning the partial or complete consumption of the starting material were carried out either by altering either the current quantity or the reaction time.

As expected, the reaction required only a catalytic amount of electricity to proceed (0.02–0.14 F/mol), while a decrease in the selectivity was noticed on extending the reaction time (Table 2, entries 2–4).

Thus, the reaction performed under the conditions reported in Table 2 (entry 2) yielded the addition product in 93% isolated yield with complete conversion of the starting material, showing the best result in terms of efficiency and chemoselectivity.

Table 1. Electrochemically-induced Michael addition of **1a** to MVK: electricity dependence

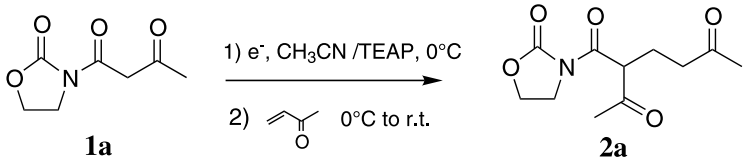
Entry[a]	Charge (F/mol)	**2a** yield (%)[b]	**1a** conv. (%)[c]
1	0.025	44	50
2	0.05	65	88
3	0.08	74	100
4	0.11	79	100
5	0.14	80	100

[a] General electrolysis conditions: two compartments cell, Pt anode and cathode. **1a** (1 mmol)+CH_3CN (15 ml)+Et_4NClO_4 (0.6 mmol), galvanostatic control, current density 10 mA/cm^2. Reaction temperature: 0°C→rt. Reaction time: 3 h.
[b] The yields refer to chromatographically pure **2a**.
[c] The conversions are calculated on the recovered, chromatographically pure starting material **1a**.

Table 2. Electrochemically-induced Michael addition of **1a** to MVK: reaction time dependence

Entry[a]	Reaction time (h)	**2a** yield (%)[b]
1	1	89
2	2	93
3	3	80
4	18	65

[a] General electrolysis conditions: two compartments cell, Pt anode and cathode. **1a** (1 mmol)+CH_3CN (15 ml)+Et_4NClO_4 (0.6 mmol), galvanostatic control, current density 10 mA/cm^2. Electrolyses stopped after consumption of 14×10^{-2} Faraday/mol of **1a**. Reaction temperature: 0°C→rt.
[b] The yields refer to chromatographically pure **2a**.



1a **2a**

Scheme 1.

It should be noted that in all cases, the α-monoaddition product was the only product detectable by ^{1}H NMR analysis of the crude mixtures, while no by-products arising from either double-addition, electroreduction of the carbonyl functionalities, or nucleophilic attack by the cyanomethyl anion (which may form in the cathodic solution)[13] were observed.

2.2. Electrochemically-promoted addition of enantiopure acetoacetic derivatives

To assess the generality of the procedure and more especially, to ascertain whether this electrochemical process was a practical method for stereoselective Michael addition, a series of enantiopure acetoacetic derivatives (**1b–f**)[12] were synthesized and submitted to the reaction conditions reported in Table 3.

The acetoacetates of Oppolzer's sultam and Evans' oxazolidin-2-ones afforded the addition products in good to excellent yields, with remarkable diastereoisomeric excesses. In contrast, the use of D-ribonolactone as a chiral inductor led to a significant decrease in the chemoselectivity and diastereoselectivity (Table 3, entry 14).

Lower chemical yield was also observed on using a stoichiometric amount of electricity (Table 3, entry 7).

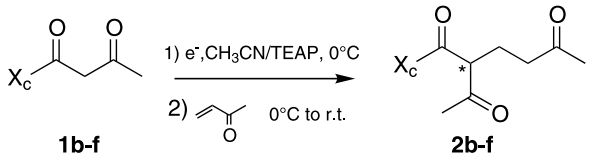
Interesting results were obtained on performing the Michael addition of the acetoacetyl derivative **1b**. The immediate quenching of the reaction (as soon as the GC–MS analysis indicated the consumption of the starting material) led to the addition products in 85% isolated yield and 71:29 d.r. (Table 3, entry 1), while a quasi-reverse diastereoselectivity (33:67 d.r.) was obtained when the reaction mixture was maintained under the electrochemical conditions for 18 h (Table 3, entry 6) or on a slight increase of the applied electrical charge (Table 3, entry 2).

Since a prolonged reaction time, as well as an increasing of the current quantity would promote diastereomeric equilibration, we propose that, at first, the less stable isomer (identified as the kinetic product) is mainly produced. The following thermodynamic equilibration would eventually lead to the predominance of the thermodynamically favored product.

The absolute configurations of the two stereoisomers of **2b** cannot be assigned at this stage. However, ab initio HF/3-21G calculations for the two isomers showed calculated heats of formation differing by ~14 kcal/mol in favour of the epimer having the *S* configuration at the newly created stereogenic center.

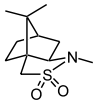
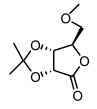
As others factors might affect the stereoselectivity of the addition, we investigated the steric hindrance effects of the substituent at C(4) of the oxazolidin-2-one moiety. As shown in Table 3, the phenyl and benzyl substituted analogs react to give products with very poor diastereomeric excesses, while a marked improvement was observed when an isopropyl substituent was present oxazolidin-2-one residue.

No improvement in the diastereoselectivity was observed on performing the reaction at –20°C (Table 3, entry 12, Scheme 2).



Scheme 2.

Table 3. Electrochemically-induced Michael addition of chiral **1b–f** to MVK

Entry	X_c	Charge F/mol	Reaction Time (h)	2 Yield (%)[a]	2 d.r.[b]
1[c]	 **1b**	0.14	4	85	71:29
2[d]	**1b**	0.20	6	78	33:67
3	**1b**	0.12	3	84 (13)	65:35
4	**1b**	0.14	3.5	77 (21)	72:28
5	**1b**	0.14	6	85	53:47
6	**1b**	0.14	18	48	33:67
7	**1b**	1.0	1	-	
8	 **1c**	0.14	2.5	98	73:27
9	**1c**	0.14	3	98	72:28
10	**1c**	0.14	14	100	72:28
11	 **1d**	0.14	3	85	63:37
12[e]	**1d**	1.0	18	35 (55)	60:40
13	 **1e**	0.14	3	94	61:39
14	 **1f**	0.10	3	37[f]	55:45

[a] Yields refer to isolated products. Yields in parentheses refer to recovered starting materials.
[b] As regard compound **2e**, the absolute configuration at the newly created stereogenic center of the major stereoisomer has been established as *R* by comparison of the optical rotation with the one reported in the literature (Ref. 5). By analogy, we assumed the same configuration *R* for the major epimer of **2c** and the opposite configuration *S* for the major epimer of **2d**.
[c] Electrolysis performed in a solution 0.05M TEAP in CH_3CN.
[d] Electrolysis performed in a solution 0.1M TEAP in CH_3CN.
[e] Reaction performed at –20°C.
[f] In this case, double-adduct was also isolated in 35% yield.

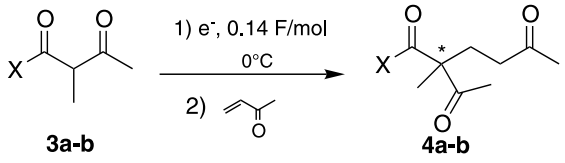
2.3. Electrochemically-promoted addition of enantiopure α-methyl acetoacetic derivatives

The potential of this electrochemically-based methodology was then further explored for the stereocontrolled construction of stereogenic quaternary carbon centers (QCCs), a topic of great interest in organic synthesis.

In this case, the problems related to the possible epimerization due to the presence of an enolizable intercarbonyl proton are obviously circumvented, but their configurations cannot be regarded as definitively locked since a racemization process might take place via retro-Michael reaction. Thus, several examples of racemization processes at QCCs of Michael adducts have been reported recently.[14] We must therefore assume that in this case, mild and carefully controlled reaction conditions, work-up and purification procedures are required to prevent loss of diastereoselectivity.

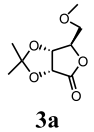
Our objective was to achieve a stereoselective C–C bond formation exploiting the pre-existing stereocenters in the starting substrates, again under electrochemical, metal-free conditions.

As shown in Table 4, the chiral substrate **3a** provided the addition product in 62% yield and 65:35 d.r. Moreover, although the stereoselectivity of the process increased with descending temperature, the use of lower temperatures compromised the yield of the reaction.



Scheme 3.

Table 4. Electrochemically-induced Michael addition of **3** to MVK

Entry	X	T (°C)	Reac. Time (h)	4 Yield (%)	4 d.r.
1	 **3a**	0	0.5	62	65:35
2	**3a**	-30	3	62	75:25
3[a]	**3a**	-60	6	53[b]	83:17
4[a,c]	 **3b**	-60	48	-	

[a] In this entry propionitrile has been used as solvent. [b]Yield is calculated on recovered starting material (47%). [c] In this entry total unreacted starting material was recovered.

Various attempts to carry out the Michael addition on the chiral (2*R*)-methyl *N*-acetoacetyloxazolidin-2-one **3b** gave unsatisfactory results. In fact, no addition product was observed after 2 days by performing the reaction at −60°C (or at −20°C), while very poor conversion (<30%) and stereoselectivity (52:48 d.r.) was obtained at room temperature.

3. Conclusion

In summary, we have shown an electrocatalytic approach to chiral enolates, which was successfully used in the Michael addition to MVK. With respect to the metal-catalyzed reaction, the electrochemical methodology offers the advantages of milder conditions, and short reaction times. Good to excellent yields and chemoselectivities were obtained by electrolysis under galvanostatic conditions, avoiding either metal or basic catalysts and, as a consequence, easy set-up and work-up procedures were established. Regarding the stereochemical aspects of the process, despite the fact that the reactions were completed in the absence of a chelating counterion,[15] moderate to high stereoselectivities were obtained solely by virtue of the stereodirecting influence of the existing stereocenters in the enolate molecule.

4. Experimental

4.1. General

The electrochemical apparatus, the cells, NMR and polarimeter instruments used in this study have been described elsewhere.[10]

Dry acetonitrile (Lab-scan, anhydroscan) was used as received, while propionitrile was freshly distilled twice from CaH_2. Tetraethylammonium perchlorate (TEAP) was purified as already described.[10] Chromatography was performed with silica gel (70–230 mesh Merck). TLC analysis was carried out on Merck Kieselgel F_{254} plates. I_2, vanillin and UV light were used as detector systems.

4.2. Electrolyses and conjugate addition to methyl vinyl ketone. General procedure

A solution of **1a–f** or **3a–b** (1 mmol) in anhydrous acetonitrile (15 mL of 0.02 M acetonitrile solution of TEAP) was electrolysed at 0°C, under galvanostatic control ($I=10$ mA cm^{-2}) in a divided cell (platinum gauze cathode and anode). At the end of the electrolysis, methyl vinyl ketone (1.5 equiv.) was added to the cathodic solution and the reaction stirred, under an argon atmosphere, until TLC disappearance of the starting material. The mixture was then concentrated in vacuo and the resulting oil purified by silica gel chromatography.

4.2.1. Isolated products. The starting materials **1e**,[5] **1f**[16] and **3a**[16] the addition products **2e**[16] and **4a**[17] gave spectral data and optical rotations according to the literature.

4.2.2. 3-Acetoacetyl-1,3-oxazolidin-2-one, 1a. Colorless solid, mp 61–63°C; ^{1}H NMR δ ($CDCl_3$): 2.25 (s, 3H); 4.00 (s, 2H); 4.02 (t, 2H, $J=4.0$ Hz); 4.43 (t, 2H, $J=4.0$ Hz). ^{13}C NMR δ ($CDCl_3$): 201.0; 179.8; 166.4; 62.2; 50.9; 42.1; 30.1. Anal. calcd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18; O, 37.39. Found: C, 49.20; H, 5.20; N, 8.10; O, 37.50%.

4.2.3. 4-[(6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]-4-oxobutan-2-one, 1b. Colorless solid, mp 74–76°C; $[\alpha]_D=-79.7$ (*c* 0.715, AcOEt); two tautomeric forms, spectroscopic data for the ketonic form: ^{1}H NMR δ ($CDCl_3$): 4.00 (d, 1H, $J=16.8$ Hz) 3.87–3.83 (m, 1H); 3.65 (d, 1H, $J=16.8$ Hz); 3.44 (apparent dd, 2H, $J_1=13.7$ Hz, $J_2=3.7$ Hz); 2.23 (s, 3H); 2.12–1.88 (m, 5H); 1.40–1.13 (m, 2H); 1.05 (s, 3H); 0.95 (s, 3H). ^{13}C NMR δ ($CDCl_3$): 199.8; 164.6; 65.01; 52.7; 50.7; 48.6; 47.7; 44.4; 38.0; 32.6; 30.2; 26.4; 20.5; 19.9. Anal. calcd for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68; O, 21.38; S, 10.71. Found: C, 56.22; H, 6.91; N, 4.72; O, 21.36; S, 10.79%.

4.2.4. (4*S*)-3-Acetoacetyl-4-isopropyl-1,3-oxazolidin-2-one, 1c. Colorless solid, mp 53–55°C; $[\alpha]_D=+58.3$ (*c* 0.72, AcOEt); ^{1}H NMR δ ($CDCl_3$): 4.48–4.41 (m, 1H); 4.40–4.24 (m, 2H); 4.22–3.89 (m, 2H); 2.51–2.33 (m, 1H); 2.26 (s, 3H); 0.92 (d, 3H, $J=2.9$ Hz); 0.89 (d, 3H, $J=2.9$ Hz). ^{13}C NMR δ ($CDCl_3$): 200.9; 166.4; 154.3; 63.6; 58.4; 51.4; 30.0; 28.3; 17.9; 14.5. Anal. calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57; O, 30.01. Found: C, 56.40; H, 6.98; N, 6.55; O, 30.07%.

4.2.5. (4*R*)-3-Acetoacetyl-4-phenyl-1,3-oxazolidin-2-one, 1d. Colorless solid, mp 113–114°C; $[\alpha]_D=-78$ (*c* 1.01, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$): 7.39–7.32 (m, 5H); 5.44 (dd, 1H, $J_1=3.7$ Hz; $J_2=8.8$ Hz); 4.68 (t, 1H, $J=8.8$ Hz); 4.21 (dd, 1H, $J_1=3.7$ Hz, $J_2=8.8$ Hz); 4.00 (s, 2H); 2.25 (s, 3H).

^{13}C NMR δ ($CDCl_3$): 201.2; 165.9; 154.0; 138.6; 129.1; 128.7; 125.9; 70.3; 57.3; 51.3, 30.1. Anal. calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67; O, 25.88. Found: C, 63.21; H, 5.30; N, 5.60; O, 25.89%.

4.2.6. 3[(2-Oxo-1,3-oxazolidin-3-yl)carbonyl]heptane-2,6-dione, 2a. Very dense oil. ^{1}H NMR δ ($CDCl_3$): 4.51–4.38 (m, 5H); 4.01–3.95 (m, 2H); 2.52 (t, 2H, $J=7.0$ Hz); 2.26 (s, 3H); 2.07 (s, 3H). ^{13}C NMR δ ($CDCl_3$): 205.5; 204.3; 169.0; 153.7; 62.3; 57.3; 42.3; 40.8; 29.8; 28.7; 20.8. Anal. calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81; O, 33.16. Found: C, 54.82; H, 6.30; N, 5.82; O, 33.06%.

4.2.7. 3{[(6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3a,6 - methano - 2,1 - benzisothiazol - 1(4*H*) - yl]carbonyl}-heptane-2,6-dione, 2b. Inseparable mixture of epimers as a very dense oil. Spectroscopic data for the major diastereoisomer (Table 3, entry 1): ^{1}H NMR δ ($CDCl_3$): 4.05 (t, 1H, $J=6.7$ Hz); 3.85 (t, 1H, $J=6.7$ Hz); 3.49 (d, 2H, $J=4.5$ Hz); 2.51–2.49 (m, 2H); 2.48–1.75 (m, 7H); 2.25 (s, 3H); 2.10 (s, 3H); 1.50–1.25 (m, 2H), 1.13 (s, 3H); 0.95 (s, 3H). ^{13}C NMR δ ($CDCl_3$): 207.0; 201.5; 168.7; 65.4; 57.7; 52.9; 48.3; 47.7; 44.5; 40.5; 38.2; 32.8; 29.7; 29.1; 26.3; 23.0; 20.7; 19.8.

4.2.8. 3-{[(4*S*)-4-Isopropyl-2-oxo-1,3-oxazolidin-3-yl]-carbonyl}heptane-2,6-dione, 2c. **Major diastereoisomer (4*S*,3*R*)**: very dense oil. $[\alpha]_D=-12.9$ (*c* 0.695, AcOEt) ^{1}H NMR δ ($CDCl_3$): 4.50–4.44 (m, 1H); 4.42–4.33 (m, 1H); 4.29–4.15 (m, 2H); 2.53 (t, 2H, $J=7.0$ Hz); 2.47–2.37 (m, 1H); 2.35 (s, 3H); 2.12–2.02 (m, 2H); 2.09 (s, 3H); 0.87 (dd, 6H, $J_1=7.0$ Hz, $J_2=4.0$ Hz). ^{13}C NMR δ ($CDCl_3$): 207.5; 204.1; 168.9; 154.1; 63.6; 58.5; 57.4; 40.8; 29.8; 28.7; 28.3; 20.7; 17.8; 14.4. Anal. calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94; O, 28.24. Found: C, 59.42; H, 7.41; N, 5.03; O, 28.14%.

Minor diastereoisomer (4*S*,3*S*): colorless solid, mp 78.8–79.9°C; $[\alpha]_D=+130.6$ (*c* 0.735, AcOEt); ^{1}H NMR δ ($CDCl_3$): 4.50–4.44 (m, 1H); 4.42–4.33 (m, 1H); 4.29–4.15 (m, 2H); 2.53 (t, 2H, $J=7.0$ Hz); 2.47–2.37 (m, 1H); 2.35 (s, 3H); 2.12–2.02 (m, 2H); 2.09 (s, 3H); 0.87 (dd, 6H, $J_1=7.0$ Hz, $J_2=4.0$ Hz). ^{13}C NMR δ ($CDCl_3$): 207.4; 204.4; 169.0; 154.3; 63.7; 58.6; 57.8; 40.9; 29.6; 29.3; 28.4; 21.2; 17.9; 14.7. Anal. calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94; O, 28.24. Found: C, 59.39; H, 7.42; N, 5.00; O, 28.19%.

4.2.9. 3-{[(4*R*)-2-Oxo-4-phenyl-1,3-oxazolidin-3-yl]carbonyl}heptane-2,6-dione, 2d. **Major diastereoisomer (4*R*,3*S*)**: very dense oil; $[\alpha]_D=-39$ (*c* 1.04, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$): 7.40–7.30 (m, 5H); 5.26 (dd, 1H, $J_1=8.8$ Hz, $J_2=4.0$ Hz); 4.70 (dd, 1H, $J_1=8.8$ Hz, $J_2=4.7$ Hz); 4.59 (t, 1H, $J=6.3$ Hz); 4.28 (dd, 1H, $J_1=8.8$ Hz, $J_2=4.0$ Hz); 2.37 (m, 2H); 2.34 (s, 3H); 2.06 (m, 2H); 2.02 (s, 3H). ^{13}C NMR δ ($CDCl_3$): 207.2; 204.2; 168.5; 153.8; 138.8; 129.0; 128.6 (2C); 125.9; 125.8; 70.0; 57.8; 57.3; 40.4; 28.7; 28.6; 20.9. Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41; O, 25.21. Found: C, 64.41; H, 6.10; N, 4.45; O, 25.04%.

Minor diastereoisomer (4*R*,3*R*): very dense oil; $[\alpha]_D=+114$ (*c* 0.47, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$): 7.40–7.30 (m, 5H); 5.42 (dd, 1H, $J_1=8.8$ Hz, $J_2=4.0$ Hz); 4.70 (t, 1H, $J=8.8$ Hz); 4.55 (dd, 1H, $J_1=7.5$ Hz, $J_2=4.7$ Hz); 4.24 (dd, 1H, $J_1=8.8$ Hz, $J_2=4.0$ Hz); 2.54 (t, 2H, $J=7.0$ Hz); 2.31 (s, 3H); 2.10 (s, 3H); 2.06 (m, 2H). ^{13}C NMR δ ($CDCl_3$): 207.5; 204.0; 168.5; 153.8; 138.3; 128.9; 128.5; 125.5; 70.3; 57.5; 57.3; 40.5; 29.7; 28.6; 20.6. Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41; O, 25.21. Found: C, 64.38; H, 6.00; N, 4.47; O, 25.15%.

4.2.10. 2-[2,3-*O*-Isopropylidene-D-ribonic-γ-lactone]-acetyl-5-oxo hexanoate, 2f. Inseparable mixture of epimers as a pale yellow oil. Spectroscopic data for the major diastereoisomer (Table 3, entry 14): ^{1}H NMR δ ($CDCl_3$): 4.74–4.71 (m, 2H); 4.70–4.66 (m, 1H); 4.50–4.15 (m, 2H); 3.51–3.45 (m, 1H); 2.51–2.45 (m, 2H); 2.16 (s, 3H); 2.07 (s, 3H); 2.25–1.90 (m, 2H); 1.41 (s, 3H); 1.33 (s, 3H); ^{13}C NMR δ ($CDCl_3$): 207.2; 202.9; 173.4; 168.6; 113.8; 79.6; 77.6; 76.4; 64.1; 57.9; 40.1; 29.9; 26.6 (2C); 25.4; 21.6.

4.2.11. 3-[2-Methyl-3-oxobutanoyl]-(4*R*)-phenyl-1,3-oxazolidin-2-one, 3b. (The title compound was prepared according to the Ref. 11. The mixture of epimers (d.r. = 60:40) was separated by silica gel chromatography and the major diastereoisomer used as the starting material as reported in Scheme 3). Colorless solid, mp 129.5–130.9°C; $[\alpha]_D = -29.4$ (*c* 0.71, AcOEt); ^{1}H NMR δ ($CDCl_3$): 7.43–7.24 (m, 5H); 5.41 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 4.0$ Hz); 4.67 (t, 1H, $J = 4.5$ Hz); 4.55 (q, 1H, $J = 7.2$ Hz); 4.20 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 4.0$ Hz); 2.27 (s, 3H); 1.32 (d, 3H, $J = 7.2$ Hz). ^{13}C NMR δ ($CDCl_3$): 204.8; 169.4; 154.0; 138.4; 129.1; 128.6 (2C); 125.8 (2C); 70.4; 57.8; 53.1; 28.2; 12.2. Anal. calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; O, 24.49. Found: C, 64.41; H, 5.71; N, 5.42; O, 24.46%.

Acknowledgements

The authors wish to thank Dr. Fabio Ramondo, Mr. Antonio Ficara for technical assistance, and MURST (Cofin 2000) for financial support.

References

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series, Pergamon: Oxford, 1992; Vol. 9 and references cited therein.
2. For a review, see: Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259–1266.
3. Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*: *Building Blocks and Fine Chemicals*; Wiley-VCH, 1998 and references cited therein.
4. (a) Taber, D. F.; Mack, J. F.; Rheingold, A. L.; Geib, S. J. *J. Org. Chem.* **1989**, *54*, 3831–3836; (b) Yamamoto, K.; Iijima, M.; Ogimura, Y. *Tetrahedron Lett.* **1982**, *23*, 3711; (c) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212.
5. Clariana, J.; Galvéz, N.; Marchi, C.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **1999**, *55*, 7331–7344.
6. (a) Monte, W. T.; Baizer, M. M.; Little, R. D. *J. Org. Chem.* **1983**, *48*, 803–806; (b) Baizer, M. M.; Chruma, J. L.; White, D. A. *Tetrahedron Lett.* **1973**, 5209–5212.
7. (a) Niyazymbetov, M. E.; Evans, D. H. *J. Org. Chem.* **1993**, *58*, 779–783; (b) Petrosyan, V. A. *Russ. Chem. Bull.* **1995**, *44*, 1411–1422.
8. Samet, A. V.; Niyazymbetov, M. E.; Semenov, V. V.; Laikhter, A. L.; Evans, D. H. *J. Org. Chem.* **1996**, *61*, 8786–8791.
9. Feroci, M.; Inesi, A.; Palombi, L.; Sotgiu, G. *J. Org. Chem.* **2002**, *67*, 1719–1721.
10. Feroci, M.; Inesi, A.; Palombi, L.; Rossi, L. *Tetrahedron: Asymmetry* **2001**, *12*, 2331–2335.
11. Palombi, L.; Feroci, M.; Orsini, M.; Rossi, L.; Inesi, A. *Tetrahedron Lett.* **2002**, *43*, 2881–2884.
12. Substrates **1a–f** were prepared in a single step according to the procedure reported in the following references: (a) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105–5108; (b) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431–35; (c) Clemens, R. J.; Witzeman, J. A. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186–93.
13. Lund, H. *Organic Electrochemistry*; Lund, H.; Hammerich, O., Eds.; Marcel Dekker: New York, 2001; 264 and references cited therein.
14. Tan, K.; Alvarez, R.; Nour, M.; Cavé, C.; Chiaroni, A.; Riche, C.; d'Angelo, J. *Tetrahedron Lett.* **2001**, *42*, 5021–5023.
15. As also reported in Ref. 4a, though a chiral inductor on the acetoacetic skeleton may selectively shield one face of the enolate molecule, such blocking does not necessarily impart selectivity to the bond-forming reaction when an ammonium counterion (which has to be considered non-chelating), is used.
16. Moreno-Manas, M.; Trepat, E.; Sebastian, R. M.; Vallribera, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4211–4224.
17. Lumbierres, M.; Marchi, C.; Moreno-Manas, M.; Sebastian, R. M.; Vallribera, A.; Lago, E.; Molins, E. *Eur. J. Org. Chem.* **2001**, 2321–2328.