Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4223–4229

TETRAHEDRON

Enantioselective alkylation and protonation of prochiral enolates in the asymmetric synthesis of β-amino acids☆

Omar Muñoz-Muñiz and Eusebio Juaristi*

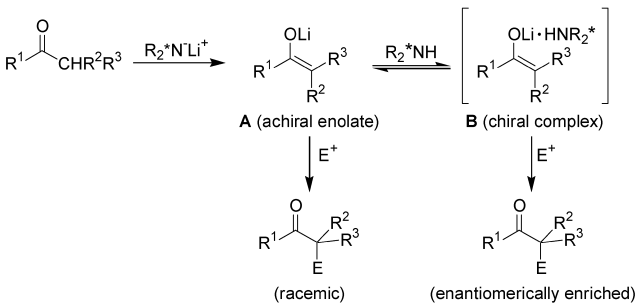
Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, D.F., Mexico

Received 30 January 2003; revised 6 March 2003; accepted 6 March 2003

Abstract—Achiral 1-benzoyl-3-methylperhydropyrimidin-4-one (**1**) was deemed a useful, potential precursor for the enantioselective synthesis of α-substituted β-amino acids. Pyrimidinone **1** was prepared from inexpensive β-aminopropanoic acid in 62% overall yield. Prochiral enolate derivative **1** -Li was alkylated in good yield and moderate enantioselectivity in the presence of chiral amines (*S*)-**8**, (*S*,*S*)-**9**, (*S*,*S*)-**10**, or (−)-sparteine. The enantioselectivity of the alkylation process is highest in toluene as the solvent and in the presence of lithium bromide as additive. The racemic alkylated derivatives **2** and **3** were readily metallated with LDA to give prochiral enolates **2**-Li and **3**-Li, that were reprotonated with novel chiral phenolic acids (*S*)-**11**, (*S*,*S*)-**12**, (*S*)-**13**, and (*S*,*S*)-**14** in moderate enantioselectivity in the case of **2**-Li and good enantioselectivity in the case of **3**-Li. The acid (6N HCl) hydrolysis of enantioenriched **2** and **3** proceeded in good yield and without racemization to afford α-alkyl-β-amino acids **4** and **5**, respectively. © 2003 Published by Elsevier Science Ltd.

1. Introduction

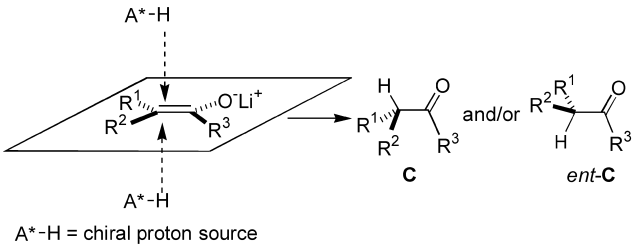
The development of highly diastereoselective α-alkylation reactions of carbonyl and related compounds is one of the most important methods in asymmetric synthesis.[2] According to Scheme 1, it is possible to develop *enantioselective* alkylation reactions in which, instead of binding covalently a chiral auxiliary (which requires a removal later on) a chiral amine concomitantly generated with the lithium enolate from a carbonyl compound and $R_2^*N^-Li^+$ is temporarily joined through a complexation that causes two achiral reagents to give enantiomerically enriched products.[3] The potential of this approach has been exploited by several research groups.[4]



Scheme 1.

Achiral enolate **A** can in principle be protonated enantioselectively by reaction with chiral proton sources, to afford non-racemic derivatives (Scheme 2). This conceptually simple approach (enantiotopic faces being distinguished by chiral reagents[5]) has been confirmed by Duhamel,[6] Fehr,[7] Vedejs,[8] and others.[9]

With the above information at hand, we undertook the studies reported herein: (1) enantioselective alkylation of prochiral enolate **1**-Li (Scheme 3(a)) and (2) enantioselective protonation of enolates **2**-Li and **3**-Li (Scheme 3(b)). Enantiomerically pure alkylated pyrimidinones **2** and **3** should afford the desired α-substituted β-amino acids **4** and **5** (Scheme 3).[10]



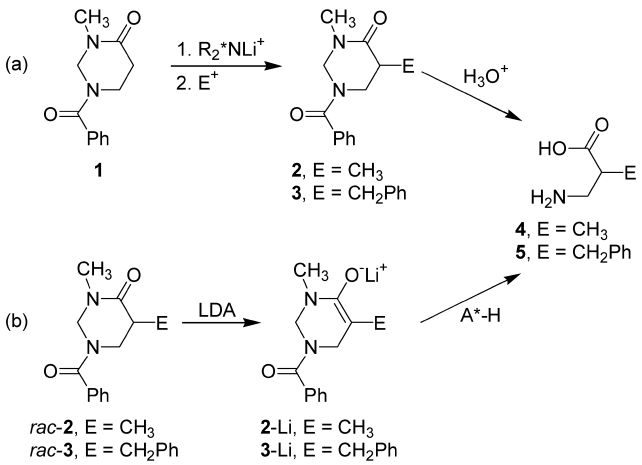
Scheme 2.

☆ See Ref. 1.

Keywords: amino acids and derivatives; stereoselective alkylations; enantioselective protonations; chiral bases; solvent and salt effects.

* Corresponding author. Tel.: +52-55-57473722; fax: +52-55-57477113; e-mail: juaristi@relaq.mx

0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4020(03)00578-7



Scheme 3.

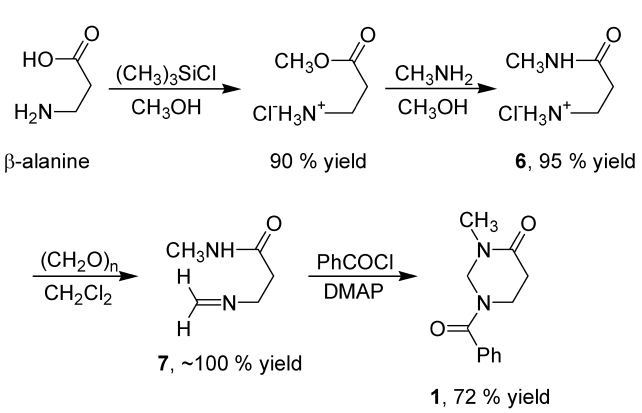
2. Results and discussion

2.1. Synthesis of 1-benzoyl-3-methylperhydropyrimidin-4-one, 1

The heterocycle **1** was prepared from β-alanine by initial conversion of its methyl ester to the corresponding *N*-methylamide **6**,[11] which formed a Schiff base with paraformaldehyde.[12] Imine **7** was then treated with benzoyl chloride in the presence of 4-dimethylaminopyridine (DMAP) to give the desired perhydropyrimidinone **1** in good yield overall (Scheme 4).[13]

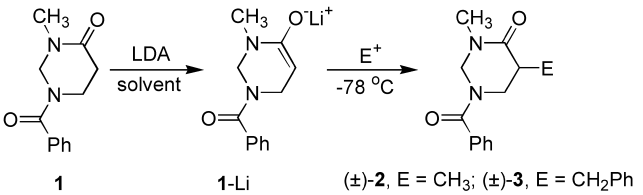
2.2. Solvent effect on the alkylation reaction, 1-Li→2 or 3

We first established the efficiency of the alkylation reaction of pyrimidinone enolate **1**-Li (obtained by metallation of **1** with lithium diisopropylamide, LDA, as base) with methyl iodide and benzyl bromide as electrophiles. Particularly interesting is the comparison of poorly coordinating solvents such as toluene, methylene chloride, and methyl *tert*-butyl ether[14] with the good coordinating THF. Our observations are collected in Table 1, and it can be appreciated that the alkylation reaction proceeds in very good yields both in THF and toluene. This latter solvent was then selected for the subsequent studies, since THF can compete with amine ligands for lithium cation coordination, and this could prevent asymmetric induction.[15]



Scheme 4.

Table 1. Solvent effect on the alkylation reaction of pyrimidinone **1** with methyl iodide and benzyl bromide



Entry	Solvent	EX	Yield (%)
1	THF	CH_3I	87
2	Toluene	CH_3I	84
3	MTBE[a]	CH_3I	42
4	CH_2Cl_2	CH_3I	69
5	THF	$PhCH_2Br$	91
6	Toluene	$PhCH_2Br$	90
7	MTBE[a]	$PhCH_2Br$	56
8	CH_2Cl_2	$PhCH_2Br$	65

[a] MTBE=methyl *tert*-butyl ether.

2.3. Enantioselective alkylation of prochiral pyrimidinone enolate 1-Li in the presence of chiral amines

Chiral amines **8**–**10** (Chart 1) incorporating the (*S*)-α-phenylethylamino group[16–19] were chosen to explore potential stereoinduction in the alkylation of enolate **1**-Li, according to the working hypothesis advanced in Scheme 1.

In the event, lithium amides (*S*)-**8**-Li, (*S*,*S*)-**9**-Li, and (*S*,*S*)-**10**-Li were prepared by metallation of the corresponding secondary amine with one equivalent of butyllithium. The required pyrimidinone enolate **1**-Li was then obtained upon treatment of heterocycle **1** with chiral bases **8**–**10**-Li in

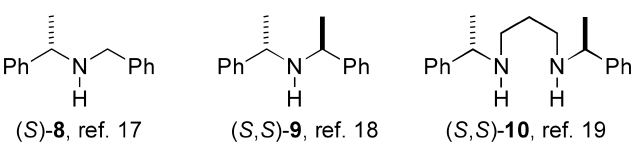
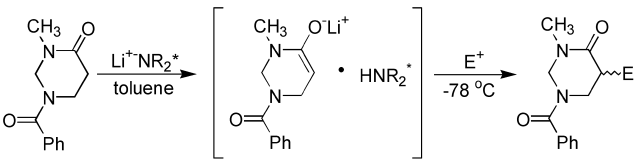


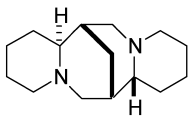
Chart 1.

Table 2. Enantioselective alkylation of enolate **1**-Li in the presence of chiral amines **8**–**10** and (−)-sparteine



Entry	Chiral amine	EX	Yield (%)	e.r.	Major enantiomer
1	(*S*)-**8**	CH_3I	70	47:53	(*R*)
2	(*S*,*S*)-**9**	CH_3I	85	41:59	(*R*)
3	(*S*,*S*)-**10**	CH_3I	75	63:37	(*S*)
4	(−)-Sparteine	CH_3I	90	67:33	(*S*)
5	(*S*)-**8**	$PhCH_2Br$	81	46:54	(*R*)
6	(*S*,*S*)-**9**	$PhCH_2Br$	92	39:61	(*R*)
7	(*S*,*S*)-**10**	$PhCH_2Br$	86	64:36	(*S*)
8	(−)-Sparteine	$PhCH_2Br$	88	70:30	(*S*)

Molar concentration of **1**: $4.6–7.6\times10^{-3}$ M. A 1:1 chiral diamine–butyllithium complex was used.



(–)-sparteine

Chart 2.

toluene solvent. The alkylation reactions were carried out at −78°C and enantiomeric ratios were determined by comparison of optical rotations with those of enantiopure standards (see below).

Table 2 collects the results of alkylation of enolate **1**-Li in the presence of chiral amines **8**–**10**. For comparison purposes, Table 2 also includes the results of methylation and benzylation in the presence of (−)-sparteine (Chart 2), a chiral diamine that has received considerable attention in the area of enantioselective alkylations.[20]

Salient observations are the opposite stereoinductions encountered with monodentate ligands (*S*)-**8** and (*S*,*S*)-**9** versus bidentate diamine ligands (*S*,*S*)-**10** and (−)-sparteine. Indeed, low and unlike[21] enantioinduction is found with the former whereas higher, like[21] enantioinduction is seen with the latter. Among the two monoamines (*S*)-**8** and (*S*,*S*)-**9**, the latter induces higher enantioselectivities (compare entries 2 and 6 with entries 1 and 5 in Table 2), probably as consequence of the presence of C_2 symmetry in (*S*,*S*)-**9**.[22] Nevertheless, asymmetric (−)-sparteine afforded better enantioselectivities than C_2-symmetric (*S*,*S*)-**10**, as can be appreciated from comparison of entries 4 and 8 with entries 3 and 7 in Table 2.

2.4. Salt (lithium bromide) effects on the enantioselective alkylation of enolate 1-Li

Evidence has accumulated in the last decade or so, that the presence of 'inert' salts can have a remarkable effect on the stereochemical outcome of enolate alkylation reactions.[3,4d,9c,22–24] Thus, it was deemed of interest to examine the effect of LiBr addition to the reaction of enolate **1**-Li with methyl iodide or benzyl bromide, in the presence of chiral ligands (*S*,*S*)-**10** and (−)-sparteine. Table 3 collects the results of this study. Although moderately, it is seen that enantioselectivities did improve when the alkylation reaction is carried out in the presence of LiBr (26–41% ee without salt, 34–50% ee with salt).

2.5. Enantioselective protonation of prochiral enolates 2-Li and 3-Li

Racemic alkylated pyrimidinones (±)-**2** and (±)-**3** (Table 1) were treated with the achiral base LDA to give prochiral enolates **2**-Li and **3**-Li, which were then reprotonated with novel chiral Bronsted acids **11**–**14** (Chart 3).

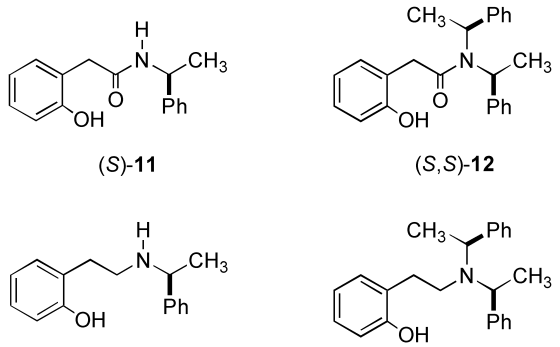
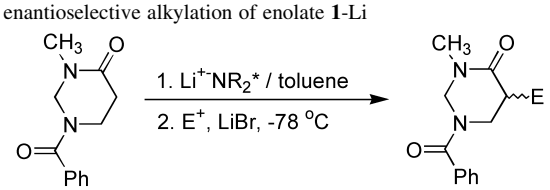


Chart 3.

As anticipated,[5–9] enantiomerically enriched heterocycles **2** and **3** were produced in good yields (Table 4). Highest enantioselectivities (53–68% ee) were observed in the protonation of benzylated **3**-Li relative to **2**-Li (compare entries 5–8 with entries 1–4 in Table 4), with best results arising from protonation with chiral phenolic amides (*S*)-**11** and (*S*,*S*)-**12**.

The higher degree of enantioselectivity achieved in the protonation of benzylated **3**-Li relative to methylated **2**-Li may originate from increased rigidity present in the former enolate, as evidenced from molecular modeling studies at the ab initio level and within the frame of density functional theory (DFT) at the B3LYP/6-31G(d) level.[25] Figure 1 presents the geometry-optimised structure for

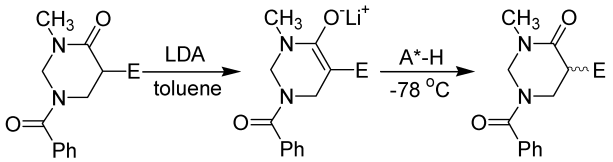
Table 3. Salt (lithium bromide) effect on the enantioselective alkylation of enolate **1**-Li



1 **2** or **3**

Entry	Ligand	LiBr (equiv.)	EX	Yield (%)	e.r.	Major enantiomer
1	(*S*,*S*)-**10**	1	CH_3I	79	69:31	(*S*)
2	(*S*,*S*)-**10**	6	CH_3I	77	70:30	(*S*)
3	(*S*,*S*)-**10**	1	$PhCH_2Br$	82	69:31	(*S*)
4	(*S*,*S*)-**10**	6	$PhCH_2Br$	80	73:27	(*S*)
5	(−)-Sparteine	1	CH_3I	71	70:30	(*S*)
6	(−)-Sparteine	6	CH_3I	76	74:26	(*S*)
7	(−)-Sparteine	1	$PhCH_2Br$	81	67:33	(*S*)
8	(−)-Sparteine	6	$PhCH_2Br$	75	75:25	(*S*)

Table 4. Enantioselective protonation of prochiral enolates **2**-Li and **3**-Li with chiral acids



Entry	E	A*–H	Yield (%)	e.r.	Major enantiomer
1	CH_3	(*S*)-**11**	88	64:36	(*S*)
2	CH_3	(*S*,*S*)-**12**	80	68:32	(*S*)
3	CH_3	(*S*)-**13**	90	60:40	(*S*)
4	CH_3	(*S*,*S*)-**14**	84	63:35	(*S*)
5	$PhCH_2$	(*S*)-**11**	90	81:19	(*S*)
6	$PhCH_2$	(*S*,*S*)-**12**	89	84:16	(*S*)
7	$PhCH_2$	(*S*)-**13**	87	77:23	(*S*)
8	$PhCH_2$	(*S*,*S*)-**14**	92	80:20	(*S*)

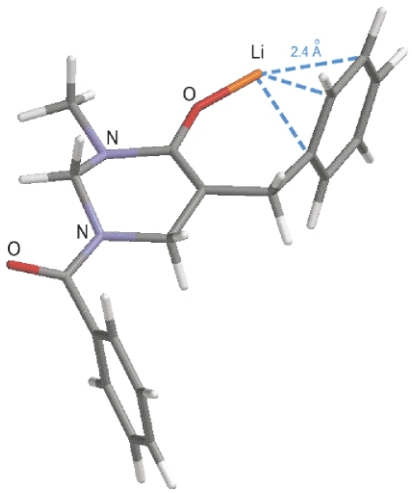
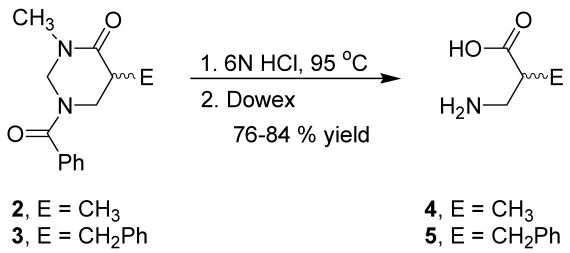


Figure 1. Global energy minimum geometry of enolate **3**-Li at B3LYP/6-31G(d) level.

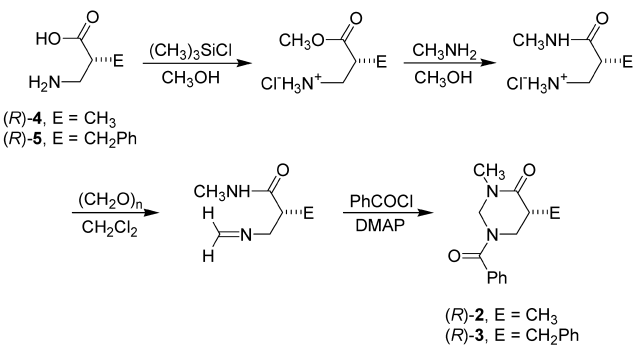
enolate (*S*)-**3**-Li. The most interesting finding is that the global minimum shows that lithium is bridged both to the enolate oxygen and to the phenyl ring in a bridged structure that resembles allyllithium.[24a,26] It is plausible that this conformationally rigid enolate affords a more defined transition structure favoring protonation on the *Re* face of the enolate, and providing (*S*)-**3** as the major enantiomeric product. By contrast, the lithium cation in enolate **2**-Li is expected to be more mobile, leading to several transition structures during protonation, and therefore to lower enantioselectivity.

2.6. Assignment of absolute configuration in alkylated products 2 and 3

Hydrolysis of alkylated pyrimidinones **2** and **3** required exposure to 6N HCl with heating to 95°C for 12–24 h (Scheme 5). Isolation of the free α-alkyl-β-aminopropanoic acid **4** or **5** in ion-exchange resin permitted comparison of optical rotation data,[2g] and thus correlation of configuration.



Scheme 5.



Scheme 6.

Alternatively, α-substituted β-amino acids **4** and **5** of known configuration[2g] were converted into enantiopure standards (*R*)-**2** and (*R*)-**3**, according to the synthetic route outlined in Scheme 6.[11–13]

3. Conclusions

β-Alanine, an inexpensive β-amino acid, was converted into achiral 1-benzoyl-3-methylperhydropyrimidin-4-one, **1**, in 62% overall yield.

In the presence of chiral amines **8**–**10** or (−)-sparteine, prochiral enolate **1**-Li was alkylated in good yields and moderate enantioselectivities. Higher enantioinduction was exhibited by bidentate diamine ligands (*S*,*S*)-**10** and (−)-sparteine, especially in the presence of LiBr salt.

Racemic alkylated pyrimidinones **2** and **3** were readily metallated with LDA, and the resulting prochiral enolates **2**-Li and **3**-Li were reprotonated with novel chiral proton sources **11**–**14**. Good enantioselectivities were observed in this protonation protocol, especially with enolate **3**-Li.

Hydrolysis of enantioenriched alkylated heterocycles **2** and **3** proceeds in good yield and without racemization to afford the corresponding α-substituted β-amino acids of interest.

4. Experimental

4.1. General experimental procedures

Flasks, stirring bars, and hypodermic needles used for the reactions with organolithium compounds were dried for ca. 12 h at 120°C and allowed to cool in a desiccator over anh. $CaSO_4$. Anh. toluene, tetrahydrofuran (THF) and methyl

tert-butyl ether (MTBE) were obtained by distillation from benzophenone ketyl. Methylene chloride was dried over CaH_2 and then distilled at reduced pressure. Lithium bromide was dried at 150°C for 5 days. The BuLi employed was titrated according to the method we developed.[27] TLC: DC-F_{254} Plate, detection by UV light and iodine. Flash column chromatography: silica gel (0.040–0.063 mm). Optical rotations were measured in a polarimeter using the sodium D-line (589 nm). Melting points are not corrected. ^{1}H NMR spectra: 400 MHz. ^{13}C NMR spectra: 100 MHz. Chemical shifts (δ) in ppm downfield from internal TMS reference; the coupling constants (J) are given in Hz.

4.1.1. General procedure for the preparation of 1-benzoyl-3-methyl-tetrahydro-pyrimidin-4-one, 1. A 100 mL three-necked flask provided with a magnetic stirrer and addition funnel was loaded with 3-amino-propanoic acid (8.9 g, 0.1 mol) in 45 mL of methanol at 0°C. Freshly distilled chlorotrimethylsilane (14 mL, 0.2 mol) was added slowly, and the resulting solution was stirred for 8 h at room temperature and at 0°C overnight. Concentration in a rotary evaporator afforded the crude product that was recrystallized from MeOH to give 11.2 g (90% yield) of 3-amino-propionic acid methyl ester hydrochloride mp 89–90°C (lit.[11] mp 89–90°C). This intermediate (10 g, 7.2 mmol) was placed in a 100 mL three-necked flask provided with a magnetic stirrer, addition funnel and condenser, and then dissolved in 50 mL of methanol. The resulting solution was cooled to 0°C before the slow addition of aqueous 40% methylamine (16 mL, 0.22 mol) with continued stirring for 36 h. The solvent was removed at reduced pressure to give 9.5 g (95% yield) of **6** as a pale yellow oil. The crude product was placed in a 100 mL flask dissolved in 50 mL of $CHCl_3$ and Et_3N (19 mL, 0.14 mol), and the resulting mixture was heated to reflux with removal of water in an inverted Dean–Stark tramp during 2 h. Then, *p*-formaldehyde (6.12 g, 0.2 mol) was added and the reflux continued for 4 additional hours. The precipitate that formed was filtered, and the solvent was removed at reduced pressure to give 7.8 g of **7** (quantitative yield). This crude product was redissolved in 150 mL of toluene before the addition of 4-DMAP (4.72 g, 0.04 mol) and benzoyl chloride (5.5 mL, 0.05 mol). The reaction mixture was refluxed 4 h, then cooled to room temperature, and filtered. The filtrate was evaporated at reduced pressure to give a yellow oil residue, which was purified by flash chromatography (hexanes–ethyl acetate, 80:20) to afford a colorless oil of the desired product, **1**.[29] (7.4 g, 82% yield). ^{1}H NMR (400 MHz, DMSO-d_6, 100°C): δ 2.41 (t, J=6.6 Hz, 2H), 2.79 (s, 3H), 3.69 (t, J=6.6 Hz, 2H), 4.82 (s, 2H), 7.46 (s, 5H). ^{13}C NMR (100 MHz, DMSO-d_6, 100°C): δ 31.9, 32.2, 42.2, 60.9, 126.9, 128.5, 130.5, 130.7, 167.6, 170.3. Anal. calcd for $C_{12}H_{14}O_2N_2$: C, 66.05; H, 6.42. Found: C, 66.12; H, 6.51.

4.2. General procedure for the alkylation of 1 via enolate formation with LDA or chiral lithium amides

A solution of the appropriate amine [(i-Pr)$_2$NH, (*S*)-**8**, (*S*,*S*)-**9**, or (*S*,*S*)-**10**)] (1.1 mmol) in the selected solvent (THF, toluene, TBME, or CH_2Cl_2) was cooled to 0°C before the slow addition of BuLi (1.1 mmol, ca. 1.8 M in hexane). The resulting solution was stirred for 30 min and then cooled to −78°C before the dropwise addition of pyrimidinone **1** in the solvent used. Stirring was continued for 1 h at −78°C in order to secure the complete formation of the corresponding enolate. The alkylating agent (1.2 mmol) was then added dropwise via syringe, and the reaction mixture was stirred at −78°C for 2 h and at ambient temperature for 20 min, and finally was cooled at −78°C for 1 additional hour. At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by flash chromatography using hexanes–ethyl acetate (7:3) as eluent.

4.3. General procedure for the alkylation of 1 via enolate formation with (−)-sparteine/BuLi

To a solution of (−)-sparteine (0.6 mL, 1.1 mmol) in the selected solvent (toluene, TBME or CH_2Cl_2) at −78°C was added BuLi (1.8 M in hexane, 1.1 mmol). The reaction was stirred for 20 min at −78°C, and a solution of pyrimidinone **1** (0.22 g, 1 mmol) in the same solvent (15 mL) was added at −78°C. The resulting mixture reaction was stirred for 4 h, and then the alkylating agent (1.2 mmol) was added dropwise via syringe. The reaction mixture was stirred for 1 additional hour at −78°C and quenched with MeOH (1 mL) before the mixture was allowed to warm to room temperature. The workup procedure was similar to that described in Section 4.2.

4.4. General procedure for the alkylation of 1 in the presence of LiBr

The general procedure for enolate formation was followed as described above. Lithium bromide (1.1 or 6.1 mmol) was added before the addition of alkylating agent in 10 mL of solvent, with continued stirring for 30 min. The reaction was quenched according to the general procedure.

4.5. General procedure for the enantioselective protonation of α-alkylated pyrimidinone 2 and 3 with chiral proton sources (*S*)-11, (*S*,*S*)-12, (*S*)-13, and (*S*,*S*)-14

The general procedure for enolate formation with LDA (Section 4.2) was followed. The protonating agent (1 mmol) in 10 mL of toluene was then added dropwise via syringe, and the reaction mixture was stirred at −78°C for 1 h and quenched with MeOH (1 mL) before the mixture was allowed to warm to room temperature. The workup procedure was similar to that described above, and the residue was purified by flash chromatography using hexanes–ethyl acetate (100:0→70:30) gradient.

4.6. Preparation of enantiopure standards (*R*)-2 and (*R*)-3

Enantiopure α-alkylated-β-amino acids (*R*)-**4** and (*R*)-**5** were prepared according to the methodology described by Juaristi et al.[2g] The corresponding enantiomerically pure pyrimidinone (*R*)-**2** and (*R*)-**3** were then obtained following the synthetic procedure described in Section 4.1.1.

4.6.1. 1-Benzoyl-3,5*R*-dimethyl-tetrahydro-pyrimidin-4-one, (*R*)-4. ^{1}H NMR (400 MHz, $CDCl_3$, 60°C): δ 1.18 (d, J=7.0 Hz, 3H), 2.64 (m, 1H), 2.97 (s, 3H), 3.33 (m, 1H), 3.95 (m, 1H), 4.75 (s, 2H), 7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, 60°C): δ 16.1, 31.5, 42.1, 59.3, 61.1, 126.1, 128.3, 129.2, 134.4, 168.9, 170.8. $[\alpha]_D^{28}$=−49.5 (c=1.0, $CHCl_3$), oil. Anal. calcd for $C_{13}H_{16}O_2N_2$: C, 67.52; H, 6.42. Found: C, 67.82; H, 6.67.

4.6.2. 1-Benzoyl-5*R*-benzyl-3-methyl-tetrahydro-pyrimidin-4-one, (*R*)-5. ^{1}H NMR (400 MHz, $CDCl_3$, 60°C): δ 2.47 (m, 1H), 2.73 (m, 1H), 2.90 (s, 3H), 3.22 (m, 1H), 4.23 (m, 2H), 4.88 (s, 2H), 7.12–7.46 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, 60°C): δ 31.4, 36.3, 47.5, 49.7, 57.1, 124.9, 126.1, 127.7, 128.0, 128.5, 129.6, 134.1, 138.2, 168.9, 170.1. $[\alpha]_D^{28}$=+68.1 (c=1.3, $CHCl_3$), wax. Anal. calcd for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54. Found: C, 74.17; H, 6.63.

4.7. General procedure for the hydrolysis of alkylated pyrimidinones, (*R*)-4 and (*R*)-5

A suspension of approximately 1 mmol of α-alkylated pyrimidinone in 10 mL of 6N HCl was heated in a sealed ampule at 95°C. The solution was then allowed to cool to ambient temperature and was extracted three times with CH_2Cl_2. The aqueous phase was evaporated to afford the crude amino acid hydrochloride, which was adsorbed to acid ion-exchange resin Dowex 50W X 8. The resin was washed with distilled H_2O until the washings came out neutral, and then the free amino acid was recovered with 1N aqueous NH_3. Evaporation afforded the crystalline amino acid, which was dried under vacuum at 40°C.

4.8. Synthesis of chiral proton sources (*S*)-11, (*S*,*S*)-12, (*S*)-13, and (*S*,*S*)-14

To a 100 mL flask provided with Dean–Stark tramp and magnetic stirrer was added (2-hydroxy-phenyl)-acetic acid (4.4 g, 29 mmol) in 60 mL of toluene and catalytic amounts of *p*-TsOH. The mixture was refluxed for 4 h with removal of water and then the residual solvent was removed at reduced pressure to give 3H-benzofuran-2-one in quantitative yield (3.9 g), mp 52°C (lit.[28] mp 50–51°C). Acetamides (*S*)-**11** and (*S*,*S*)-**12** were obtained by refluxing of 3*H*-benzofuran-2-one and (*S*)-phenylethyl-amine or (*S*,*S*)-bis-phenylethylamine (equimolar amounts) in toluene. Aminoalcohols (*S*)-**13** and (*S*,*S*)-**14** were prepared by refluxing of the corresponding acetamides with $LiAlH_4$ (3.3 equiv.) in THF for 24–48 h.

4.8.1. 2-(2-Hydroxyphenyl)-*N*-(1-phenylethyl)acetamide, (*S*)-11. ^{1}H NMR (400 MHz, $CDCl_3$, 60°C): δ 1.42 (d, J=7.3 Hz, 3H), 3.55 (dd, J=11.6, 4.1 Hz, 2H), 5.04 (m, 1H), 6.89–7.32 (m, 9H), 9.96 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 40.6, 49.6, 117.6, 120.5, 121.7, 126.1, 127.5, 128.8, 129.1, 130.9, 142.5, 155.8, 177.7. $[\alpha]_D^{28}$=−34.7 (c=1.1, $CHCl_3$), mp 105°C. Anal. calcd for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 75.05; H, 6.74.

4.8.2. 2-(2-Hydroxyphenyl)-*N*,*N*-bis-(1-phenylethyl)acetamide, (*S*,*S*)-12. ^{1}H NMR (400 MHz, $CDCl_3$, 60°C): δ 1.29 (d, J=7.2 Hz, 3H), 1.37 (d, J=7.2 Hz, 3H), 3.58 (q, J=7.2 Hz, 1H), 3.70 (dd, J=11.9, 6.9 Hz, 2H) 4.21 (q, J=7.1 Hz, 1H), 7.11–7.55 (m, 14H), 9.37 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.1, 40.6, 40.8, 49.9, 50.2, 117.6, 120.4, 121.9, 127.5, 129.1, 129.2, 130.4, 142.6, 155.9, 179.8. $[\alpha]_D^{28}$=−75.4 (c=1.0 $CHCl_3$), oil. Anal. calcd for $C_{16}H_{20}ONCl$: C, 66.92; H, 7.22. Found: C, 66.62; H, 7.26.

4.8.3. 2-[2-(1-Phenyl-ethylamino)-ethyl]-phenol, (*S*)-13. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, J=6.9 Hz, 3H), 2.71–2.83 (m, 4H), 3.84 (q, J=6.9 Hz, 1H), 6.95–7.39 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 34.4, 47.7, 58.1, 117.6, 118.9, 119.0, 126.3, 126.5, 127.3, 127.6, 128.2, 128.8, 130.9, 143.2, 156.9. $[\alpha]_D^{28}$=−56.9 (c=1.5, $CHCl_3$), wax. Anal. calcd for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01. Found: C, 80.31; H, 7.18.

4.8.4. 2-{[2-Bis(1-phenyl-ethyl)-amino]-ethyl}-phenol, (*S*,*S*)-14. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J=6.9 Hz, 3H), 1.42 (d, J=6.9 Hz, 3H), 2.69–2.80 (m, 4H), 3.79 (q, J=6.9 Hz, 1H), 3.93 (q, J=6.9 Hz, 1H), 7.11–7.62 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.8, 33.7, 39.6, 46.1, 48.3, 56.5, 57.3, 116.3, 116.9, 117.7, 118.2, 118.9, 119.3, 120.1, 125.4, 126.1, 126.8, 127.5, 129.8, 133.4, 142.9, 147.3, 157.3. $[\alpha]_D^{28}$=−95.0 (c=1.1, $CHCl_3$), oil. Anal. calcd for $C_{24}H_{27}ON$: C, 83.44; H, 7.88. Found: C, 83.59; H, 7.63.

Acknowledgements

We are indebted to Dr Jaime Escalante for the preparation of pyrimidinone **1**, Q. Fred García Flores for the elemental analysis and to Conacyt-México for financial support via grant 33023-E.

References

1. Enantioselective synthesis of β-amino acids, **14**. For part 13, see: Gutiérrez-García, V. M.; Reyes-Rangel, G.; Muñoz-Muñiz, O.; Juaristi, E. *Helv. Chim. Acta* **2002**, *85*, 4189.
2. (a) Eliel, E. L.; Koskimies, J. K.; Lohri, B.; Frazee, W. J.; Morris-Natschke, S.; Lynch, J. E.; Soai, K. In *Asymmetric Reactions and Processes*; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, 1982. (b) Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983–1984; Vol. 3, pp 1–110. (c) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (d) Enders, D.; Bettray, W.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 1322 and references cited therein. (e) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241. (f) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. (g) Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233. (h) León-Romo, J. L.; Virues, C. I.; Aviña, J.; Regla, I.; Juaristi, E. *Chirality* **2002**, *14*, 144.
3. (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.
4. (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*,

755. (b) Duhamel, L.; Plaquevent, J. C. *Tetrahedron Lett.* **1980**, *21*, 2521. (c) Hogeveen, H.; Menge, W. M. P. B. *Tetrahedron Lett.* **1986**, *27*, 2767. (d) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657. (e) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. (f) Sato, D.; Kawasaki, H.; Schimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761. (g) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825. (h) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (i) Hoppe, D.; Woltering, M. J.; Oestreich, M.; Froehlich, R. *Helv. Chim. Acta* **1999**, *82*, 1860. (j) Hilmersson, G.; Ahlberg, P.; Davidsson, Ö. *J. Am. Chem. Soc.* **1996**, *118*, 3539. (k) Marukata, M.; Yasukata, T.; Aoki, T.; Nakajima, M.; Koga, K. *Tetrahedron* **1998**, *54*, 2449. (l) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (m) Matsuo, J.; Odashima, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 345. (n) Hussein, M. A.; Iida, A.; Tomioka, K. *Tetrahedron* **1999**, *55*, 11219. (o) Hodgson, D. M.; Maxwell, C. R.; Matthews, I. R. *Tetrahedron: Asymmetry* **1999**, *10*, 1847. (p) Greenhalgh, D. A.; Simpkins, N. S. *Synlett* **2002**, 2074. (q) Honda, T.; Kimura, N. *Org. Lett.* **2002**, *4*, 4567. (r) O'Brien, P. Tetrahedron Symposium-in-Print; *Tetrahedron* **2002**, *58*, 4567–4734.

5. (a) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.
6. (a) Duhamel, L.; Plaquevent, J.-C. *J. Am. Chem. Soc.* **1978**, *100*, 7415. (b) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J. C. *Bull. Soc. Chim. Fr.* **1984**, 421.
7. (a) Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909. (b) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566.
8. (a) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175. (b) Vedejs, E.; Kruger, A. W.; Suna, E. *J. Org. Chem.* **1999**, *64*, 7863.
9. (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (b) Kosugi, H.; Hoshino, K.; Uda, H. *Tetrahedron Lett.* **1997**, *38*, 6861. (c) Asensio, G.; Aleman, P.; Gil, J.; Domingo, L. R.; Medio-Simon, M. *J. Org. Chem.* **1998**, *63*, 9342. (d) Yanagisawa, A.; Watanabe, T.; Kikuchi, T.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 2979. (e) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **1998**, *39*, 8691. (f) Aboulhoda, S. J.; Reiners, I.; Wilken, J.; Henin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1847. (g) Matsumoto, K.; Tsutsumi, S.; Ihori, T.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 9614. (h) Fujii, I.; Lerner, R. A.; Janda, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 8528. (i) Potin, D.; Williams, K.; Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1420. (j) Landaiz, Y.; Zekri, E. *Eur. J., Org. Chem.* **2002**, 4037. (k) Roy, O.; Riahia, A.; Hénin, F.; Muzart, J. *Eur. J. Org. Chem.* **2002**, 3986. (l) Eames, J. *Eur. J. Org. Chem.* **2002**, 393. (m) Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *Tetrahedron* **2002**, *58*, 4669. (n) Munoz-Muniz, O.; Juaristi, E. *Tetrahedron Lett.* **2003**, *44*, 2023.
10. The enantioselective synthesis of β-amino acids is of continuing interest in modern organic chemistry: (a) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *23*, 117. (d) In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley: New York, 1997. (e) Juaristi, E.; López-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983. (f) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
11. Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553.
12. Escalante, J.; Juaristi, E. *Tetrahedron Lett.* **1995**, *36*, 4397.
13. Juaristi, E.; Escalante, J. *J. Org. Chem.* **1993**, *58*, 2282.
14. (a) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567. (b) Streitwieser, A.; Juaristi, E.; Kim, Y. J.; Pugh, J. K. *Org. Lett.* **2000**, *2*, 3739.
15. (a) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448. (b) Abbotto, A.; Streitwieser, A. *J. Am. Chem. Soc.* **1995**, *117*, 6358.
16. (a) Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715. (b) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.
17. Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243.
18. Overberger, C. G.; Marullo, N. P.; Hiskey, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374.
19. Hulst, R.; de Vries, K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699. See, also: Juaristi, E.; Hernández-Rodríguez, M.; López-Ruiz, H.; Aviña, J.; Muñoz-Muñiz, O.; Hayakawa, M.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1999.
20. (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422. (b) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (c) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (d) Oestreich, M.; Froehlich, R.; Hoppe, D. *J. Org. Chem.* **1999**, *64*, 8616 and references cited therein.
21. For a definition of the like/unlike stereochemical descriptors, see: (a) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. (b) See, also: Ref. 5a, pp 52–54.
22. (a) Galiano-Roth, A. S.; Kim, Y. J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053. (b) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571. (c) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533.
23. (a) Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, *73*, 1616. (b) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465.
24. (a) Juaristi, E.; León-Romo, J. L.; Ramírez-Quirós, Y. *J. Org. Chem.* **1999**, *64*, 2914. (b) Reyes, A.; Juaristi, E. *Tetrahedron: Asymmetry* **2000**, *11*, 1411.
25. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E., Jr.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petterson, G. A.; Ayala, P.;Y.; Cui, Q.; Ortiz, J. V.; Baboul, A. G.; Stafanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, D. J.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98* (Revision A.7); Gaussian, Inc.: Pittsburgh, PA, 1998.
26. Lambert, C.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1129.
27. Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603.
28. Goncalo, P.; Roussel, C.; Melot, J. M.; Vebrel, J. *J. Chem. Soc. Perkin Trans. 2* **1999**, *10*, 2111.
29. Ramírez-Quiroz, Y.; Balderas, M.; Escalante, J.; Quintana, D.; Gallardo, I.; Madrigal, D.; Molins, E.; Juaristi, E. *J. Org. Chem.* **1999**, *64*, 8668.