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Memory of Chirality of Tertiary Aromatic Amides: A Simple and Efficient Method for the Enantioselective Synthesis of Quaternary α-Amino Acids

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Abstract: A new methodology for the asymmetric synthesis of quaternary α-substituted amino acids using memory of chirality has been developed. The strategy utilizes the dynamic axial chirality of tertiary aromatic amides to memorize the initial chirality of an α-amino acid during an enolization step. Starting from five different L-amino acids, the corresponding oxazolidin-5-ones containing a tertiary aromatic amide group have been synthesized in one step and then alkylated with various electrophiles, with good yields and enantioselectivities (up to 96% and up to >99% after recrystallization). One-step deprotection affords enantioenriched or enantiopure quaternary α-amino acids. We describe here the optimization process, the results obtained in each series and a plausible explanation, based on NMR studies, DFT calculations and crystallographic structures. The methodology presented herein constitutes an efficient synthesis of enantiopure quaternary α-amino acids (three steps only) starting from tertiary L-amino acids, without any external source of chirality.

Introduction

The conformation of a peptide is crucial for its biological activity and most small natural peptides are conformationally flexible, thus not able to adopt a secondary peptide structure. One way to restrict peptide conformation is the introduction of a side chain restricted amino acid, for instance a quaternary α-amino acid.[1] Thus, due to their biological importance, many procedures have been developed for the stereoselective synthesis of quaternary α-amino acids.[2] Typical methods involve chiral auxiliaries[3] or chiral catalysts,[4] but very few use only the chirality of the starting α-amino acids.[5] Among them are the Self Regeneration of Stereocenters, developed by D. Seebach[6] and exemplified by other groups,[7] and more recently some procedures applying a new principle, memory of chirality.[8]

A reaction proceeding with memory of chirality has been defined by Carlier as "a formal substitution at a sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system". By applying this principle, several groups succeeded in enantioselective quaternization of α-amino acids derivatives.[9] The most successful examples have been reported by Carlier, who used the intrinsic chirality of the benzodiazepine-2-one ring to obtain α,α-dialkyl amino acids enantioselectively.[12] In addition, Kawabata has performed methylation and allylation of various α-amino acids with high enantiomeric excesses.[10] Although the electrophile range is quite limited for the

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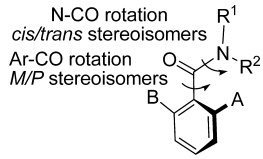


Figure 1. Tertiary aromatic amides.

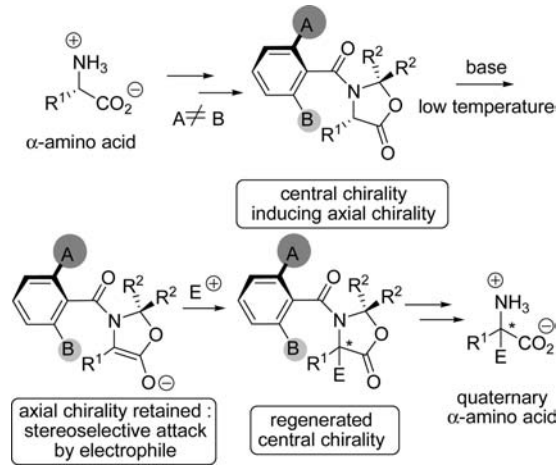
intermolecular reaction, a very efficient intramolecular alkylation reaction was developed.[11]

In order to improve these results, we thought to use the axial chirality of tertiary aromatic amides, which present two slow bond rotations (Figure 1).[13] These compounds are generally not planar and even moderate steric hindrance forces a dihedral angle of 90° on the Ar−CO bond. Subject to certain constraints of substitution pattern (A ≠ B), the two perpendicular conformers about the Ar−CO bond are enantiomeric (R^1 and R^2 achiral) or diastereomeric (R^1 or R^2 chiral), and these compounds can therefore present axial chirality.

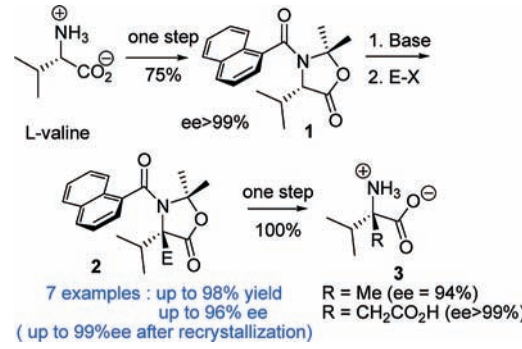
Our strategy was to introduce a tertiary aromatic amide function onto the starting α-amino acid in order to transfer the initial central chirality to an axial chirality. Due to the high rotation barriers of tertiary aromatic amides, the axial chirality should be retained during the enolization/alkylation step at low temperature and induce a stereoselective attack by the electrophile. The quaternary α-amino acid should be obtained after deprotection (Scheme 1). In order to protect both the amino and the acid groups, we chose an oxazolidin-5-one, knowing that it is easy to synthesize and to cleave.

We have successfully applied this strategy to L-valine and performed the synthesis of quaternary enantioenriched L-valine **3** in only three steps (Scheme 2).[14] We have also proposed an explanation for the observed stereoselectivity based on DFT

Scheme 1. General Strategy for the Synthesis of Enantioenriched Quaternary α-Amino Acids



Scheme 2. Synthesis of Enantioenriched Quaternary L-Valine



calculations and NMR studies.[15] Herein, we report a full article of our work, including the application of this strategy to other amino acids.

Results and Discussion

1. Optimization of Reaction Conditions Starting from L-Valine. We decided to develop our method starting from L-valine because of the steric hindrance induced by the isopropyl group and because of the biological interest of α-methylvaline.[16] We have chosen oxazolidinones **4** arising from formaldehyde (R^2 = H) or **5** from acetone (R^2 = Me) and also tested several aromatic groups. Compounds **4** were synthesized following a known two-step procedure: initial condensation of L-valine with an aromatic acyl chloride,[17] and then formation of the oxazolidinone ring by heating the resulting compound **6** in toluene with paraformaldehyde (Scheme 3).[18] Unfortunately, we could not avoid slight deterioration of the enantiomeric excess[19]

(9) (a) Kolaczkowski, L.; Barnes, D. M. *Org. Lett.* **2007**, *9*, 3029–3032. (b) Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1067–1072. (c) Giese, B.; Wettstein, P.; Stähelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessing, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586–2587. (d) Bonache, M. A.; Lopez, P.; Martin-Martinez, M.; Garcia-Lopez, M. T.; Cativiela, C.; Gonzalez-Muniz, R. *Tetrahedron* **2006**, *62*, 130–138. (e) Bonache, M. A.; Cativiela, C.; Garcia-Lopez, M. T.; Gonzalez-Muniz, R. *Tetrahedron Lett.* **2006**, *47*, 5883–5887.

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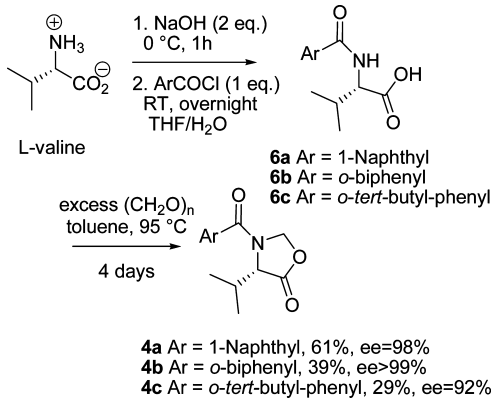
(17) *o*-Phenyl-benzoyl chloride was synthesized from the corresponding acid (oxalyl chloride 3 equiv, catalytic DMF, dichloromethane, 0 °C, 1 h, 96%); *o*-*tert*-butyl-benzoyl chloride was synthesized by S_NAr with *tert*-butyllithium onto 2-fluorobenzoïc acid: Gohier, F.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2003**, *5*, 1919–1922. followed by reflux in thionyl chloride (75% overall yield).

(18) Ben-Ishai, D. *J. Am. Chem. Soc.* **1957**, *79*, 5736–5738.

(19) All enantiomeric excesses are determined by chiral stationary-phase HPLC.

Scheme 3. Synthesis of Oxazolidinone **4**



Scheme 4. Synthesis of Oxazolidinones **1** and **5a**,**b**

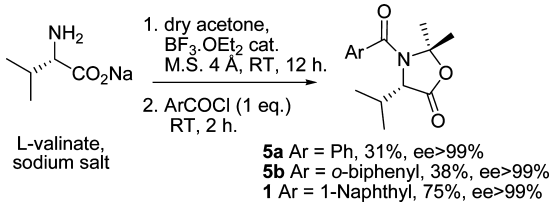
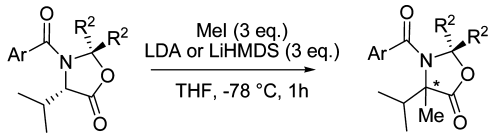


Table 1. In Situ Methylation of Oxazolidines **1**, **4** and **5**



1 or **4a**, **b**, **c** or **5b** → **2a** or **7a**, **b**, **c** or **8b**

entry	R^2	Ar	substrate (ee %)	product	base	yield[a] (%)	ee[b] (%)
1	H	1-naphthyl	**4a** (98%)	**7a**	LiHMDS	36	0
2	H	*o*-biphenyl	**4b** (>99%)	**7b**	LDA	20	11
3	H	*o*-*t*-Bu-phenyl	**4c** (92%)	**7c**	LDA	45	56
4	Me	*o*-biphenyl	**5b** (>99%)	**8b**	LDA	5[c]	32
5	Me	1-naphthyl	**1** (>99%)	**2a**	LDA	14	70

[a] Isolated yield. [b] Enantiomeric excess, determined by chiral stationary-phase HPLC. [c] Conversion, determined by chiral stationary-phase HPLC.

(except for compound **4b**, because it was crystalline). We obtained the expected compounds **4** in moderate yields (addition of catalytic *p*-toluenesulfonic acid increased yields but also racemization).

Oxazolidinones **1**, **5a**, **b** were synthesized without racemization in one step from sodium L-valinate by modifying a procedure described by Seebach (Scheme 4).[20] Unfortunately, we were unable to synthesize the *o*-*tert*-butyl-benzoyl derivative by applying this method.

We next performed *in situ* methylation (introduction of electrophile before base) to force alkylation to occur as soon as the enolate is formed. In this case, racemization (i.e., Ar−CO rotation) of the enolate should be limited. Deprotonation was achieved with LiHMDS or LDA when LiHMDS was not strong enough (Table 1). The major drawback of this method is the likely competitive alkylation of the base, resulting in decreased yields.

Compound **7a** was obtained in racemic form, and compound **7b**, with a low enantiomeric excess. In order to understand these

(20) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243–1250.

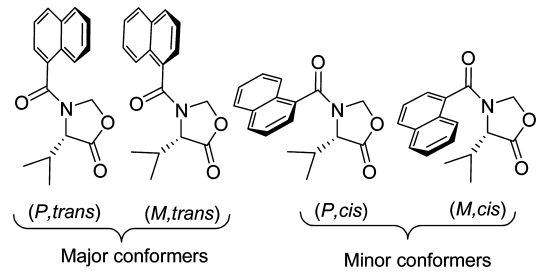


Figure 2. Four conformers of compound **4a**.

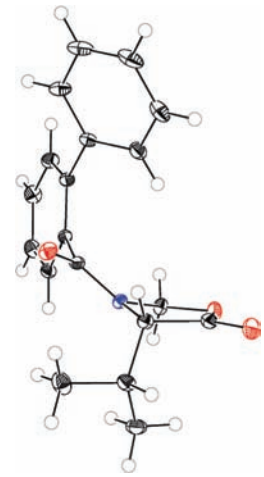


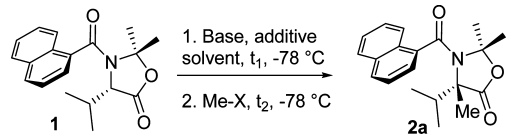
Figure 3. ORTEP plot for X-ray crystal structure of compound **4b**. Ellipsoids are drawn at the 50% probability level.

disappointing results, we obtained ^{1}H NMR spectra in $CDCl_3$ of the starting oxazolidinones **4a** and **4b** at low temperature. For compound **4a**, four conformers are observable (Figure 2), the *trans*-conformers (carbonyl oriented toward the isopropyl group) being the major ones (*cis/trans* assignment can be easily made by chemical shift comparison, N-substituents *cis* to the carbonyl group being shifted downfield relative to those of N-substituents *cis* to the aromatic ring[21]). For compound **4b**, two conformers (ratio 1/0.2) are observable, the *trans*-conformer being again the major one. Moreover, in the crystallographical structure of compound **4b**, the conformation of the tertiary aromatic amide was determined to be (*P,trans*) (Figure 3), suggesting once again that *trans*-conformers are favored. These preferred *trans*-conformations force the aromatic group to be oriented far away from the asymmetric center and could explain the low enantioselectivities obtained. For compound **4c**, the situation is slightly different, because at room temperature, the four conformers are already clearly defined, with one highly favored one (*trans*-conformer). This indicates that the Ar−CO and N−CO rotation barriers are much higher than in the former cases. Thus, in this case, the higher enantiomeric excess of 56% likely results from increased hindrance and/or increased rotation barriers.

For compounds **5b** and **1**, introduction of a quaternary center on the oxazolidinone (derived from acetone) induces a radical change in *cis/trans* orientation. For compound **5b**, at room temperature, only two conformers are observable (^{1}H NMR spectrum in $CDCl_3$), one of which is very predominant (ratio 100:4). As no crystallographic structure can be obtained for

(21) Lewin, A. H.; Frucht, M.; Chen, K. V. J.; Benedetti, E.; di Blasio, B. *Tetrahedron* **1975**, *31*, 207–215.

Table 2. Screening for Methylation Reaction Conditions of Compound **1**[a]



entry	solvent	base[b] (equiv)	additive (equiv)	t_1 (min)	X (equiv)	t_2 (min)	conv (%)[c]	ee (%)[c]
1	THF	LDA (3)	−	0[d]	I (3)	60	14	70
2	THF	LDA (3)	−	0[d]	I (6)	60	(9[e])	64
3	THF	LDA (3)	−	0[d]	I (30)	60	(13[e])	81
4	THF	LDA (3)	−	3	I (30)	60	67(56[e])	65
5	THF	LDA (3)	−	30	I (30)	60	(56[e])	32
6	THF	LDA (3)	DME (6)	3	I (30)	60	49	70
7	THF	KDA[f] (3)	DME (6)	3	I (30)	60	56[g]	72
8	THF	KHMDS (3)	−	0[d]	I (6)	60	20	85
9	THF	KHMDS (3)	−	4	I (30)	10	49	66
10	THF	KHMDS (3)	DME (6)	4	I (30)	10	57	74
11	THF	KHMDS (3)	DME (6)	10	I (30)	10	100	57
12	THF	KHMDS (3)	18-c-6 (3)	10	I (30)	10	100	8
13	THF	KHMDS (3)	18-c-6 (3)	1	I (30)	10	95	33
14	THF	KHMDS (3)	TMEDA (3)	10	I (30)	10	64	72
15	THF	KHMDS (3)	−	10	I (30)	10	78	50
16	Et_2O	KHMDS (3)	DME (6)	10	I (30)	10	87	79
17	Et_2O	KHMDS (3)	DME (6) DMPU (6)[h]	10	I (5)	10	71	80
18	Et_2O[i]	KHMDS (1.5)	DME (3) DMPU (3)[h]	10	I (5)	10	88(74[e])	78
19	Et_2O[i]	KHMDS (1.5)	DME (3)	3	OTf (3)	10	64	88
20	Et_2O[i]	KHMDS (1.5)	DME (3)	8	OTf (5)	10	95(78[e])	82
21	Et_2O[i]	KHMDS (1.5)	DME (3)	10	OTf (2)	10	99(72[e])	82
22	Et_2O[i,j]	KHMDS (1.5)	DME (3)	8	OTf (5)	10	93	85
23	Et_2O[i,k]	KHMDS (1.5)	DME (3)	8	OTf (5)	10	99	54
24	Et_2O[i,l]	KHMDS (1.5)	DME (3)	8	OTf (5)	10	82	83

[a] Unless specified, the concentration of **1** was 0.07 mol·L^{-1}, and a mixture of base and additive was added *via* canula at −78 °C to compound **1**. [b] KHMDS 0.5 M in toluene, LDA prepared from *n*BuLi in hexane and diisopropylamine. [c] Determined by chiral stationary-phase HPLC. [d] Electrophile *in situ*. [e] Isolated yield. [f] Synthesized *in situ* from LDA and *t*-BuOK. [g] Nucleophilic attack of KDA was also observed. [h] Added with electrophile. [i] Concentration of **1** was 0.15 mol·L^{-1}. [j] Reaction at −86 °C. [k] Reaction at −60 °C. [l] Crystal dissolution at −78 °C.

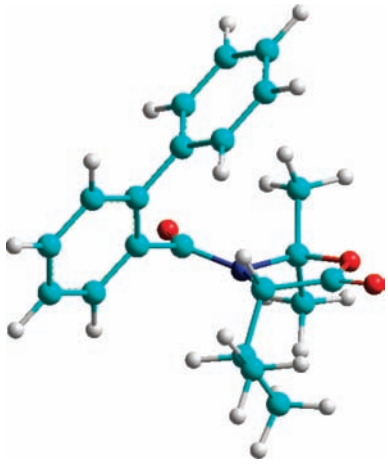


Figure 4. Minimized structure of compound **5b**.

compound **5b**, we attempted to determine the major conformer observed (^{1}H NMR spectrum in $CDCl_3$) by performing computational studies. In accordance with the experimental data, all three semiempirical methods tested (MNDO, AM1 and PM3) for energy minimization calculation[22] gave the lowest energy for the (*M,cis*)-conformer (Figure 4). Steric hindrance due to the second aromatic ring (located right over the labile proton), and high rotation barriers would explain why deprotonation of compound **5b** is so difficult (entry 4, Table 1).[23] Sequential deprotonation/methylation with KHMDS (3 equiv)/MeI (30 equiv) at −78 °C did not improve conversion (8%). However, performing the deprotonation for 30 min with KHMDS at −56 °C and then addition of MeI (30 equiv) gave 35% conversion but a lower ee (20%). We suppose that at higher temperature, rotation of the aromatic becomes possible and allows deprotonation of the minor conformer.

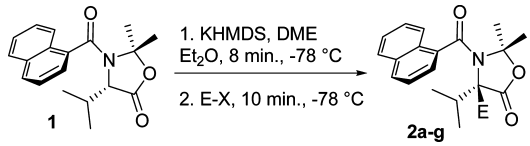
Compound **1** gave the methylated compound **2a** with the highest enantiomeric excess (70%), despite a low yield. For compound **1**, four conformers are present on the ^{1}H NMR spectrum in $CDCl_3$ at low temperature, and the *cis*-conformers are now the major ones. We have previously noticed that the crystal structure of compound **1** indicated that, in the solid state, **1** adopts a (*P,cis*)-conformation,[14] which was consistent with the major conformation adopted in $CDCl_3$ at low temperature (full ^{1}H NMR assignment of the labile proton in the four conformers was achieved by theoretical studies[15]). Thus, in the major conformer, the carbonyl group is oriented toward the more hindered quaternary center, placing the aromatic group close to the asymmetric center. This phenomenon could explain the better enantioselectivity observed.

Considering that compound **1** was easily accessible in enantiopure form and that this oxazolidinone gave methylated compound **2a** with good enantiomeric excess (despite a low yield), we decided to pursue our studies on this oxazolidinone. Base, additives, solvents, electrophiles and reaction conditions (temperature, concentration, deprotonation time or alkylation time) were then screened (Table 2).

(22) For details, see Supporting Information.

(23) At −78 °C the low ee and conversion could be eventually explained by deprotonation/alkylation of the minor conformer, which is probably a *trans* one.

Table 3. Alkylation of Compound **1**[a]



entry	electrophile	E	product	yield (%)	ee (%)[b]	recryst yield (%)	ee (%)[b]
1	MeI[c]	Me	**2a**	74	78		
2	MeOTf	Me	**2a**	78[d]	82	60	94
3	EtOTf	Et	**2b**	59	91	80	>99
4	allyl-I	allyl	**2c**	88[d]	88	67	99
5	Bn-I	Bn[e]	**2d**	72−98	73−91	85	>99
6	4-OMeBn-I	4-OMeBn	**2e**	98[d]	86	83	98
7	ethyliodoacetate	CH_2CO_2Et	**2f**	80[d]	96	89	>99
8	*t*-BuOD	D	**2g**	76[f]	93		

[a] General procedure: KHMDS (1.5 equiv, 0.5 M in toluene) diluted in DME (3 equiv) at −78 °C was added *via* canula to a solution of **1** in Et_2O at −78 °C (concentration of **1** = 0.15 mol·L^{-1}); after 8 min, electrophile (5 equiv) was rapidly added and after 10 min at −78 °C, reaction was quenched with acetic acid. [b] Determined by chiral stationary-phase HPLC. [c] DMPU (3 equiv) added with electrophile. [d] Complete conversion. [e] For unknown reasons, ee varies from 73 to 91%. [f] Percent deuteration determined by ^{1}H NMR spectroscopy.

The *in situ* reaction gave the highest enantioselectivity but low yields, and increased enolate formation time improved the yield but caused deterioration of the enantioselectivity. KHMDS gave higher yields and enantioselectivities than LDA (entries 2 and 8) and was therefore selected for further study. Yields and enantioselectivities generally increased when an additive was used. Among the additives tested, 1,2-dimethoxyethane (DME) gave the best results. Using a crown ether boosted conversion but was deleterious to the enantiomeric excess (entries 12 and 13), suggesting that the countercation has to remain in the vicinity of the enolate. Therefore, we replaced THF by a less coordinating solvent, diethyl ether. Conversion was, not surprisingly, slightly decreased but racemization of the enolate was also slowed down (entries 11 and 16). Good conversion was restored when replacing methyliodide by the more reactive methyltriflate (or by adding DMPU with methyliodide), and by increasing the concentration. Lowering the temperature (−86 °C, entry 22) did not significantly improve the enantioselectivity, and increasing the temperature was deleterious (−60 °C, entry 23). Moreover, dissolution of crystals at −78 °C (entry 24) just before the reaction did not improve enantioselectivity. The best conditions were the following: deprotonation with 1.5 equiv of KHMDS (in toluene) in diethyl ether/DME (3 equiv) for less than 10 min (a 0.15 mol·L^{-1} concentration for the enolate corresponds to a toluene/ether ratio of 55/45) and alkylation with a very reactive electrophile for 10 min (entry 20), or with a less reactive electrophile with DMPU (entry 18).

2. Alkylation of Compound 1 and Synthesis of α-Substituted L-Valine. We next applied the optimized conditions to other reactive electrophiles (Table 3): enantioselectivities exceed 73%, and yields range from 59 to 98%. Enantioselectivity can be enhanced by recrystallization for all compounds. For compounds **2d** and **2e**, the racemic compound crystallized and was removed, leading to the enantiopure compound by evaporation of the mother liquor. Moreover, analysis of deuterated compound **2g** by chiral stationary-phase HPLC indicated that deuteration proceeded with retention of configuration.

Finally, deprotection and isolation of the quaternary α-amino acid was achieved in one step. Hydrolysis of compound **2a** (ee = 94%) or **2f** (ee > 99%) in refluxing HBr 47% led quantitatively to α-methylvaline **3a** or α-isopropylaspartic acid **3f** (Scheme 5). The *S*-configuration was confirmed by comparison with the optical rotation of known compounds.[24]

Scheme 5. Access to Enantioenriched α-Substituted Amino Acids

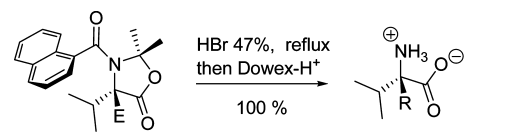
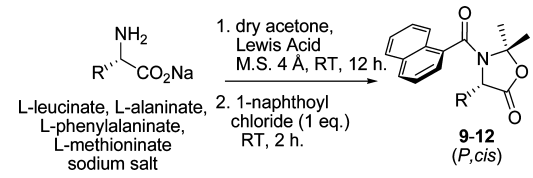


Table 4. Synthesis of Oxazolidinones **9**−**12**



entry	amino acid	R	Lewis acid	product	yield (%)	ee (%)[a]
1	L-leucine	*i*-Bu	$BF_3.OEt_2$ (cat)	**9**	49	>99
2	L-alanine	Me	$AlMe_3$ (1 equiv)	**10**	52	>99
3	L-phenylalanine	Bn	$AlMe_3$ (1 equiv)	**11**	61	>99
4	L-methionine	CH_2CH_2SMe	$AlMe_3$ (1 equiv)	**12**	46	>99

[a] Determined by chiral stationary-phase HPLC.

3. Extension to Other Amino Acids. We next wanted to extend this methodology to other amino acids. The corresponding oxazolidinones were synthesized following the same procedure (in some cases, $AlMe_3$ gave better yields than $BF_3.OEt_2$) without racemization (Table 4). Crystal structures of compounds **10**, **11** and **12**[25] show that in the solid state, they all adopt a (*P,cis*)-conformation (Figure 5).

3.1. Extension to L-Leucine. Compound **9** was not very soluble in ether, and therefore allylation of this oxazolidinone under optimized conditions gave compound **13a** in only 35% yield. Solubilization with additional DME gave alkylated compounds **13a**−**c** with high yields and enantioselectivities (Table 5).

Enantiopure quaternary α-amino acids can be synthesized following the same strategy as described above: recrystallization of compound **13c** and deprotection in refluxing HBr led quantitatively to enantiopure α-isobutylaspartic acid **14** (Scheme 6). Retention of configuration was confirmed by comparison of the optical rotation with that of a known compound.[26]

3.2. Extension to L-Alanine. Compound **10** was not very soluble in ether, and therefore supplementary DME (12 equiv) was added to perform allylation. Enantioselectivity was disappointingly low, and thus optimization of the allylation conditions was necessary (Table 6, entry 1). Replacement of ether by THF increased product solubility, and DME was no longer necessary. This led to enantiomeric excess enhancement (entries 1 and 3), and the best results were obtained by performing the reaction without toluene (entry 5). Compared with oxazolidinone **1**, the enolate arising from oxazolidinone **10** is much more configu-

(24) (a) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A.; Lapena, Y. *Tetrahedron* **1995**, *51*, 5921–5928. (b) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1987**, *28*, 2243–2246.
(25) For compound **12**, the crystallographic structure reveals eight conformers (because of the flexibility of the alkyl chain), all with (*P,cis*)-conformation.
(26) Obrecht, D.; Bohdal, J.; Daly, J.; Lehman, C.; Shoenholzer, P.; Mueller, K. *Tetrahedron* **1995**, *51*, 10883–10900.

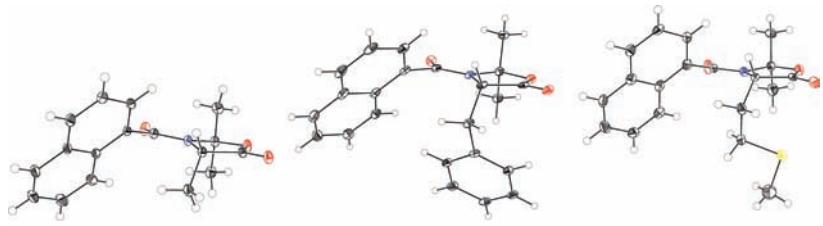
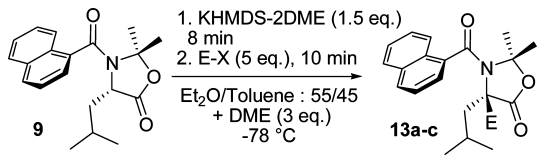


Figure 5. ORTEP plot for the X-ray crystal structure of compounds **10**, **11** and **12**. Ellipsoids are drawn at the 50% probability level.

Table 5. Alkylation of Oxazolidinone **9**



entry	E-X	E	product	yield (%)	ee (%)[a]
1	allyl-I	allyl	**13a**	88	90
2	Me-OTf	Me	**13b**	86	87
3	ethyliodoacetate	CH_2CO_2Et	**13c**	96	94

[a] Determined by chiral stationary-phase HPLC.

Scheme 6. Synthesis of (*R*)-α-Isobutylaspartic Acid

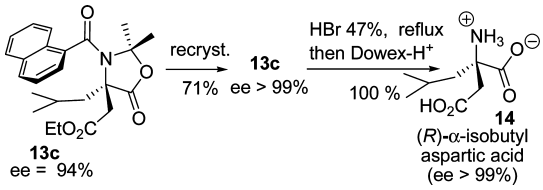
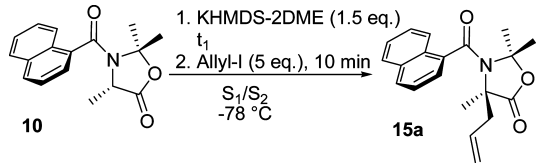


Table 6. Allylation of Oxazolidinone **10**



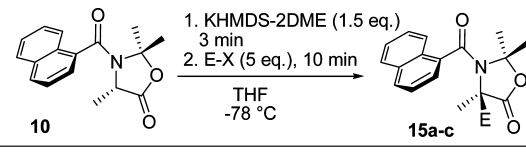
entry	solvent 1[a] (S_1)	solvent KHMDS (S_2)	S_1:S_2	t_1 (min)	conv (%)[b]	ee (%)[b]
1	Et_2O/DME (3:1)	toluene[c]	62:38	3	100	67
2	Et_2O/DME (3:1)	toluene[c]	62:38	8	100	67
3	THF	toluene[c]	55:45	3	100	74
4	THF	toluene[c]	55:45	1	86	75
5	THF	THF[d]	70:30	3	100	79
6	THF	THF[d]	70:30	8	100	79

[a] Solvent used for oxazolidinone dissolution. [b] Determined by chiral stationary-phase HPLC. [c] Commercially available KHMDS 0.5 mol·L^{-1} in toluene. [d] KHMDS 0.5 mol·L^{-1} in THF (evaporation of toluene and replacement by THF).

rationally stable: the enantiomeric excess is unchanged between 3 and 8 min deprotonation times (entries 1/2, or 5/6). Performing direct deprotonation on crystals did not induce significant changes, and we applied the optimized conditions (entry 5) to other electrophiles (Table 7).

In all cases, alkylated products **15a**−**c** were obtained in good yields and enantioselectivities. Recrystallization of compound **15c** and deprotection in refluxing HBr led quantitatively to enantiopure α-methylaspartic acid **16** (Scheme 7). Retention of configuration was confirmed by comparison of the optical rotation with that of a known compound.[24b]

Table 7. Alkylation of Oxazolidinone **10**



entry	E-X	E	product	yield (%)	ee (%)[a]
1	allyl-I	allyl	**15a**	87	79
2	Bn-Br	Bn	**15b**	82	82
3	ethyliodoacetate	CH_2CO_2Et	**15c**	94	91

[a] Determined by chiral stationary-phase HPLC.

Scheme 7. Synthesis of (*R*)-α-Methylaspartic Acid

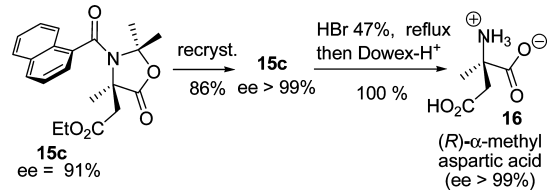
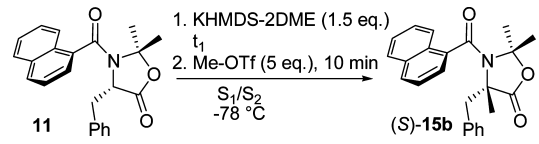


Table 8. Methylation of Oxazolidinone **11**

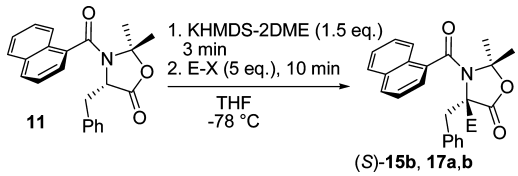


entry	solvent 1[a] (S_1)	solvent KHMDS (S_2)	S_1:S_2	t_1 (min)	conv (%)[b]	ee (%)[b]
1	Et_2O	toluene[c]	55:45	8	34	65
2	THF	toluene[c]	55:45	8	100	73
3	THF	toluene[c]	55:45	3	100	73
4	THF	THF[d]	70:30	3	100	75
5	THF/DME (1:1)	toluene[c]	55:45	3	100	67
6	THF/DME (1:1)	toluene[c]	55:45	8	100	74
7	THF/toluene (1:1)	toluene[c]	70:30	8	100	65

[a] Solvent used for oxazolidinone dissolution. [b] Determined by chiral stationary-phase HPLC. [c] Commercially available KHMDS 0.5 mol·L^{-1} in toluene. [d] KHMDS 0.5 mol·L^{-1} in THF (evaporation of toluene and replacement by THF).

3.3. Extension to L-Phenylalanine. Application of the conditions optimized for oxazolidinone **1** were not satisfying, and therefore, a change of solvent was necessary (Table 8). Chiral stationary-phase HPLC analysis showed directly (comparison with the chromatogram of compound **15b** obtained from oxazolidinone **10**) that compound **15b** is formed with retention of configuration. Compared with oxazolidinone **1**, the enolate arising from oxazolidinone **11** is much more configurationally stable: the enantiomeric excess is unchanged between 3 and 8 min deprotonation time (entries 2 and 3). Addition of supplementary DME, toluene or DMF did not improve enantioselec-

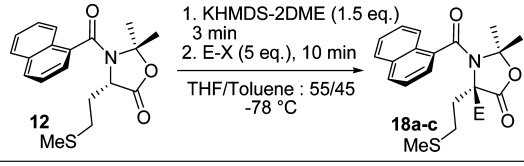
Table 9. Alkylation of Oxazolidinone **11**



entry	E-X	E	product	yield (%)	ee (%)[a]
1	MeOTf	Me	(*S*)-**15b**	88	75
2	allyl-I	allyl	**17a**	92	68
3	ethyliodoacetate	CH_2CO_2Et	**17b**	85	89

[a] Determined by chiral stationary-phase HPLC.

Table 10. Alkylation of Oxazolidinone **12**



entry	E-X	E	product	yield (%)	ee (%)[a]
1	allyl-I	allyl	**18a**	85	86
2	MeI	Me	**18b**	92	78
3	MeOTf	Me	**18b**	62	86
4	*tert*-butylbromoacetate	CH_2CO_2t-Bu	**18c**	75	91

[a] Determined by chiral stationary-phase HPLC.

tivity (entries 5−7). As for oxazolidinone **10**, best yields and enantioselectivities were obtained by removal of toluene (entry 4).

We next applied these conditions to other electrophiles (Table 9). Alkylated compounds **15b**, **17a**,**b** were obtained in good yields but slightly lower enantioselectivities.

3.4. Extension to L-Methionine. For oxazolidinone **12**, replacement of ether by THF gave better yields and enantioselectivities. Alkylation of this compound with ethyliodoacetate gave the expected product with only 16% yield because of competitive sulfur alkylation.[27] Other electrophiles gave the quaternary compounds **18a−c** in good yields (except for methyltriflate, for probably the same reason) and enantioselectivities (Table 10).

Retention of configuration was confirmed by the crystallographic structure of compound **18b** (Figure 6): absolute configuration was determined by the refinement of the Flack parameter (Flack, 1983).[28]

In conclusion, all five oxazolidinones gave alkylated compounds in high yields and enantioselectivities, with retention of configuration. Best results were obtained with ethyliodoacetate or *tert*-butylbromoacetate as electrophile, and in these cases, yields range from 75 to 96% and enantioselectivities from 89 to 96%.

4. Explanation for Observed Stereoselectivity. In order to confirm our initial hypothesis, we used the optimized conditions and performed an alkylation reaction on compound **5a** (which cannot present axial chirality around the Ar−CO bond). Only racemic product **19** was obtained in 59% yield (Scheme 8). We can conclude that there is no complex between the starting oxazolidinone and the corresponding enolate that could be responsible for asymmetric induction.

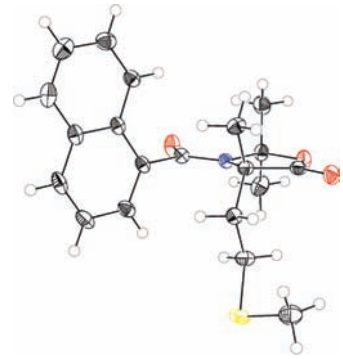


Figure 6. ORTEP plot for X-ray crystal structure of compound **18b**. Ellipsoids are drawn at the 50% probability level.

Scheme 8. Alkylation of Compound **5a**

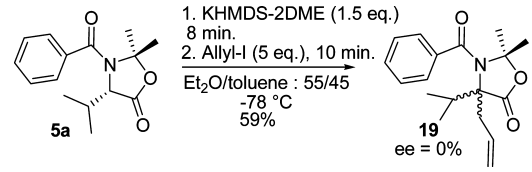


Table 11. Conformer Ratio Observed by ^{1}H NMR Spectroscopy at 195 K of Oxazolidinones **1**, **10**−**12**

entry	starting amino acid	compound	solvent	number of conformers	(*P,cis*)/(*M,cis*)[a]	*cis*/*trans*[a]
1	L-Val	**1**	THF-d_8	4	100.0/14.2	100.0/5.7
2	L-Val	**1**	Et_2O-d_{10}	4	100.0/14.2	100.0/1.7
3	L-Val	**1**	toluene-d_8/ Et_2O-d_{10} (5/6)	4	100.0/11.5	100.0/2.7
4	L-Ala	**10**	THF-d_8	4	100.0/29.0	100.0/2.0
5	L-Phe	**11**	THF-d_8	3[b]	100.0/49.8	100.0/9.9
6	L-Met	**12**	THF-d_8	4	100.0/30.1	100.0/2.2

[a] Determined by integration of the labile proton in each conformer. [b] Chemical shifts are slightly different because of the second aromatic group.

We have also previously noticed that enantioselectivity depends on temperature, deprotonation time, and solvent. Performing deprotonation on crystals or dissolution of crystals at −78 °C just before reaction produced no significant change. All these observations suggest the formation of a dynamic axial chiral enolate.

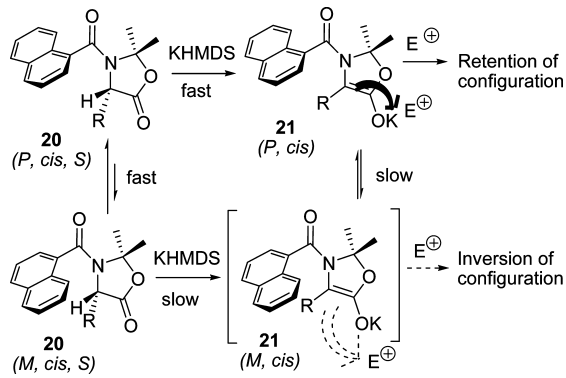
In addition, we have obtained ^{1}H NMR spectra of compounds **1**, **10**, **11** and **12** in Et_2O-d_{10} or THF-d_8 at 195 K. For compound **1**, we had previously achieved complete assignment of the labile proton in the four conformers in $CDCl_3$ by theoretical studies, and because of similarity between the spectra (for $CDCl_3$, THF, Et_2O and Et_2O/toluene), we have extended the preceding assignment to the other solvents and then to the other oxazolidinones. Therefore, we deduced the following points: in all cases, the (*P,cis*)-conformer is observed in solid state and corresponds to the major conformer in solution; the (*P,trans*)- and (*M,trans*)-conformers can often be neglected (except for compound **11**, derived from phenylalanine), and various (*P,cis*):(*M,cis*) ratios can be determined (Table 11). We also supposed that oxazolidinone **9** (derived from L-leucine) behaved in the same manner.

Since these ratios cannot explain the high conversion rates and enantioselectivities and also since reactions on crystals were unsuccessful, we suggest that a dynamic kinetic resolution is

(27) (a) Labuschagne, A. J.; Malherbe, J. S.; Meyer, C. J.; Schneider, D. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 955–961. (b) Lawecka, J.; Bujnicki, B.; Drabowicz, J.; Rykowski, A. *Tetrahedron Lett.* **2008**, *49*, 719–722.

(28) See crystallographic data in Supporting Information.

Scheme 9. Explanation of Observed Stereoselectivity



responsible for stereochemical induction (Scheme 9). Ar−CO rotation in compound **20** (between the two diastereomeric conformers (*P,cis,S*) and (*M,cis,S*)) should be faster than metalation and lead to preferential deprotonation of the (*P,cis*)-conformer in which the labile proton is more accessible. Racemization of the resulting enolate **21** (Ar−CO rotation) should be relatively slow (even very slow for enolates derived from compounds **10** and **11**), and alkylation should occur opposite to the second aromatic ring, leading to global retention of configuration. For compound **11**, the presence of a *trans*-conformer can perhaps explain the lower enantioselectivities observed.

Conclusion

In conclusion, we have demonstrated that amino acid-derived *N*-aroyloxazolidinone are valuable substrates for alkylation according to Memory of Chirality. These substrates are accessible in only one step starting from the corresponding amino acid, and their synthesis uses only simple organic compounds (naphthoyl chloride and acetone). We have developed suitable conditions for quaternization of these compounds and performed efficient alkylation with reactive electrophiles. This methodology was found to be general to several amino acids included the functionalized methionine. Thus, we have developed an efficient three-step synthesis of enantioenriched α-methylvaline (ee = 94%), α-isopropylaspartic acid (ee > 99%), α-methylaspartic acid (ee > 99%) and α-isobutylaspartic acid (ee > 99%) without an external source of chirality. Therefore, we have performed alkylation of oxazolidinones by memory of chirality as defined by Carlier, and shown the efficiency of using dynamic axial chirality of tertiary aromatic amides in the field of memory of chirality. We have also proposed an explanation for the observed stereoselectivities, based on ^{1}H NMR spectra at low temperature, DFT calculations and crystallographic structures. Further NMR and DFT studies are under investigation in our laboratory to quantify rotation barrier, as well as extension of this methodology to other amino acids, and to aldolization reactions.

Acknowledgment. This research was supported by Université de Paris-Sud, CNRS and Ministère de l'Enseignement Supérieur et de la Recherche (doctoral grant to M.B.). We thank J.-P. Baltaze and A. Dos Santos for NMR analysis.

Supporting Information Available: Crystallographic data and ^{1}H NMR at low temperature of compounds **10**, **11** and **12**, experimental details and characterization of all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

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