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Absolute Asymmetric Synthesis of Tertiary α-Amino Acids**

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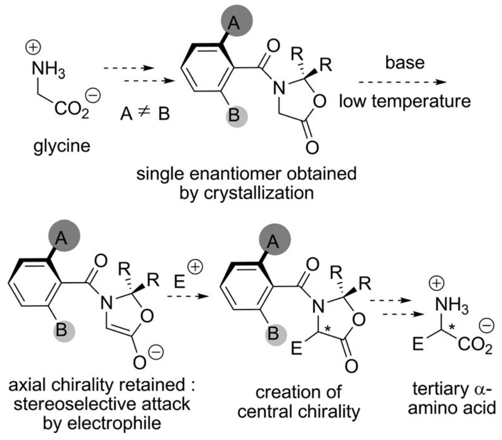
The synthesis of one enantiomer in the absence of any chiral substance is a major challenge and very attractive from both economical and conceptual points of view. This type of synthesis has been termed absolute asymmetric synthesis. Nevertheless, few examples of absolute asymmetric synthesis have been described to date.[1] Several approaches have been developed, for instance irradiation with circularly polarized light,[2] or application of rotational and magnetic forces,[3] or attrition-enhanced deracemization.[4] The most exemplified approach in organic synthesis is probably the use of chiral crystals of achiral or racemic compounds.[5] In that case, the chiral crystals arise from spontaneous crystallization of achiral compounds in a chiral conformation or from macroscopic chiral arrangement in crystals of racemic compounds. These chiral crystals can be inorganic or organic and are used in absolute asymmetric synthesis either as reactant[6] or catalyst.[7] Owing to the constraints generated by the use of crystals, only a limited number of organic reactions have been reported to date, mostly in the field of photochemical cycloaddition[8] or asymmetric autocatalysis.[9] To retain the chirality of the crystal and prevent racemization of the conformation, the reaction is often performed in solid state or after dissolution at low temperature. This latter concept has been named "frozen chirality".[10]

For a few years we have been interested in the development of asymmetric syntheses of nonproteinogenic amino acids starting from natural α-amino acids.[11] Based on our previous results,[11a–c] we wanted to tackle the great challenge of the absolute asymmetric synthesis of tertiary α-amino acids by exploiting the frozen-chirality concept. Herein, we describe for the first time a practical absolute asymmetric synthesis of tertiary α-amino acid derivatives with enantiomeric excesses up to 96% by starting from glycine, which is an achiral compound. The synthesis involves a two-step reaction (deprotonation–alkylation), using the homochirality of the starting crystal as the unique source of stereoinduction.

Our strategy relies on the use of the axial chirality of tertiary aromatic amides.[12] These compounds are generally not planar around the Ar–CO bond, and even moderate steric hindrance induces a dihedral angle of 90°. Depending on the substitution pattern (A ≠ B; Scheme 1) these compounds can therefore present axial chirality. This strategy (Scheme 1) requires the preparation of an oxazolidinone derived from glycine and the growth of a chiral crystal made up of only one enantiomer (axial chirality along the Ar–CO bond). Dissolution at low temperature should prevent rotation and subsequent racemization. Hence, this axial frozen chirality should be retained, thereby inducing stereoselective attack by electrophiles. After deprotection, various enantioenriched tertiary natural or unnatural α-amino acids would be obtained in few steps.



Scheme 1. General strategy of absolute asymmetric synthesis of tertiary α-amino acids.

After several attempts, we found that oxazolidinone **1** (A = H, B = Ph, R = Me in Scheme 1; prepared in one step from sodium glycinate) crystallized in the chiral space group $P2_12_12_1$ (Figure 1). A single crystal can be either a*R* or a*S* (axial chirality along the Ar–CO bond) with a 50% probability; both crystalline enantiomers are obtained during the same crystallization procedure. Analysis of the crystallographic structure shows that the *ortho*-phenyl group is oriented towards the acidic protons and that it hinders one of the two prochiral acidic protons (the dihedral angle between the carbonyl group and the aromatic group is 113°). Therefore, this compound seemed suitable for the planned strategy. Despite some reproducibility problems, preliminary trials showed that small crystals of this compound

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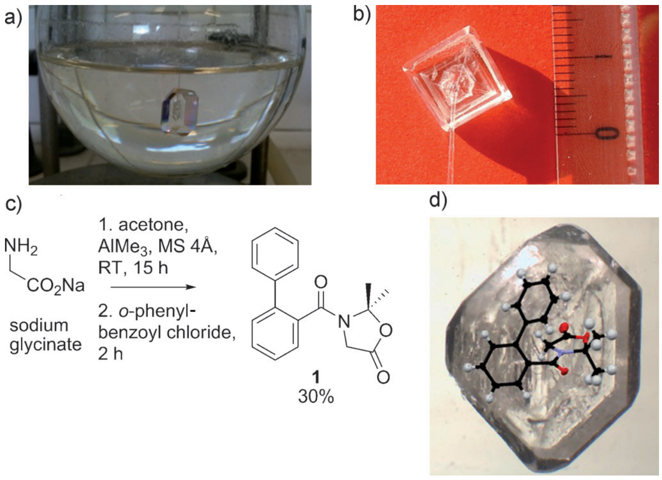
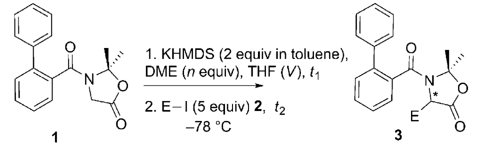


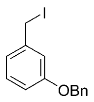
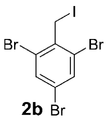
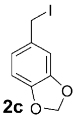
Figure 1. Compound **1**: a) Picture of crystal growth, b) picture of a large crystal of compound **1** stuck on the capillary (scale in cm), c) synthesis (MS = molecular sieves), d) picture of a small crystal superimposed with crystallographic structure (O red, N blue, H white).

can be alkylated with enantiomeric excesses up to 61%. Then, we decided to change the crystallization procedure. Small crystals of compound **1** were formed in diethyl ether and quality-checked under polarized light in a binocular microscope. A polarization microscope is the most convenient tool for analyzing the quality and size of crystals: normally, a good single crystal is well-shaped with visible planar faces and extinction of polarized light is uniform; consequently the crystal is exempt from defects or twinning problems. After this selection, a small crystal was stuck onto a capillary, dipped in a saturated solution of compound **1**, and allowed to stir gently for a couple of weeks for crystal growth. Because rotation about the Ar–CO bond is very rapid (racemization of the crystal occurs almost instantaneously after dissolution at room temperature), we are able to recrystallize the major part of the solution. Thus, a defect-free crystal of 2 g can be obtained after three weeks. After grinding into a thin powder, optimization of the alkylation step was undertaken.

Preliminary results showed that the optimal solvent was tetrahydrofuran (THF), and the optimal base was potassium hexamethyldisilylamide (KHMDS). The investigation of cosolvents showed that dimethoxyethane (DME) was the most appropriate (*N*,*N*,*N*′,*N*′-tetramethyl-ethane-1,2-diamine (TMEDA) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) did not improve the results). To ensure a rapid reaction without racemization of the initial crystal (after dissolution) or of the intermediate enolate (both issues must be avoided), the following procedure was adopted: a precooled solution of base, solvents, cosolvents, and, if possible, the electrophile was prepared, and this solution was added through a cannula directly onto the powdered crystals of oxazolidinone **1** (also cooled to −78 °C). To limit the racemization of the enolate, reactive benzylic electrophiles (with iodide as leaving group) were chosen. We favored electrophiles that could give access to biologically relevant compounds (electrophile **2a** should give access to *meta*-tyrosine,[13] **2b** to a potentially interesting analogue of phenylalanine,[14] and piperonyl iodide to 3,4-dihydroxyphenylalanine (DOPA)). For each electrophile, the cosolvent quantity, the grinding type for the substrate (manual or by ball mill), and the conditions of the reaction (concentration, deprotonation time, or alkylation time) were then screened (Table 1).

Table 1: Screening of reaction conditions for alkylation of oxazolidinone **1**.[a]

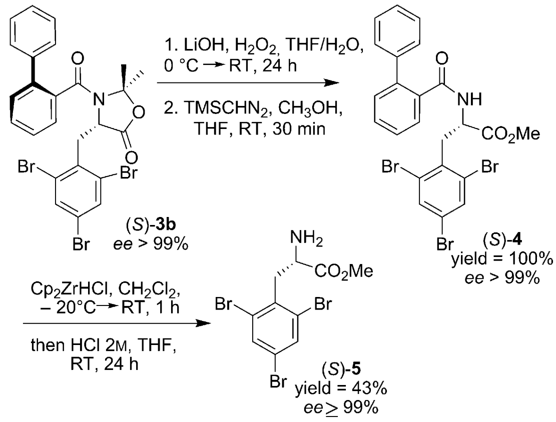


Entry	Electrophile E-I	Grinding[b]	*n* equiv of DME	*V* [mL] THF	t_1 [min]	t_2 [min]	Prod.	Yield[c] [%]	*ee*[d] [%]
1	 OBn **2a**	M	2.1	5	0	10	**3a**	45 (60)	72 (72)
2		M	2.1	5 [e]	0	10		(65)	(20)
3		M	2.1	1	0	10		(42)	(88)
4		M	30	1.2	0	10		(58)	(88)
5		M	0	1.2	0	10		(42)	(83)
6		M	2.1	1	0	180		64 (99)[f]	73 (74)
7		PBM	30	1.2	0	10		48 (74)	96
8	 **2b**	M	2.1	1.2	0.5[g]	9.5	**3b**	18	82
9		PBM	2.1	1.2	0.5	9.5		68	80
10		PBM	2.1	1.2	0.33	9.67		70	90
11		PBM	30	1.2	0.5	9.5		(90)	(50)
12		PBM	30	5	0.5	9.5		(98)	(30)
13	 **2c**	M	2.1	1.2	0	10	**3c**	(21)	(94)
14		M	2.1	5	0	10		(37)	(93)
15		PBM	2.1	1.2	0	10		50	83
16		PBM	2.1	5	0	10		57	87

[a] Unless specified, a precooled solution of KHMDS (2 equiv, 0.7 M in toluene) and additive in THF was added through a cannula at −78 °C to the powdered crystals of **1** (0.135 mmol). After t_1 min ($t_1 = 0$ means that the electrophile is in the same solution as the base), electrophile **2** (5 equiv) was added and the mixture allowed to stir for t_2 min at −78 °C. [b] M = manual grinding and PBM = grinding with a planetary ball mill of crystals of compound **1**. [c] Yields in brackets correspond to conversion, determined on the crude product by HPLC. [d] Enantiomeric excesses were determined by HPLC using a chiral stationary phase. *ee* values in brackets are determined on the crude product. Racemic mixture for HPLC references were synthesized by alkylation after previous dissolution of the crystals **1** at room temperature. [e] Reaction was performed without toluene. [f] Significant amount of dialkylated product was observed. [g] Since reaction occurred between the electrophile and the base, the electrophile was added soon after the base.

In almost all cases, high enantioselectivities can be reached but sometimes with rather low conversions. This is due to the low solubilization of the starting crystals: at the end of some experiments, white powder was still present in the reaction medium. Several approaches were envisaged to limit this problem: optimization of solvents and solubility (use of larger amount of solvents or modification of the solvents and cosolvents), increase of the alkylation time, and reduction of the size of the powder particles by grinding the crystals of compound **1** with a planetary ball mill. The comparison between entries 2, 4, and 5 shows that the presence of toluene and DME is necessary to give a high *ee* (moreover, reaction without THF, only DME, showed almost no alkylated product). Depending on the electrophile, more or less either DME or THF is beneficial to the reaction (compare entries 1 and 3, 3 and 4, 10 to 12, 13 and 14, and 15 and 16). On the one hand, an increase of the alkylation time did not have the expected effect (entry 6): it induced a second deprotonation of the alkylated compound **3a** (easier to deprotonate compared to crystals of **1**, because **3a** is already in solution), thereby resulting in racemization of **3a** and/or formation of dialkylated compound. On the other hand, the use of a planetary ball mill was very effective, and it slightly improved the conversions (compare entries 4 and 7, 8 and 9, 13 and 15, 14 and 16). Optimized conditions led to the alkylated products with enantioselectivities from 87 to 96% and yields from 48 to 70%. Moreover, recrystallization of compound **3b** in a mixture of THF and pentane afforded enantiopure crystals (*ee* > 99%, yield = 55%). Several recrystallizations of this compound were performed on different samples, and crystallographic analysis was carried out on the enantiomer that possesses the longest retention time (using HPLC with a chiral stationary phase). The absolute configuration of this enantiomer was given by crystallographic structure determination (*R* configuration). For practical reasons, the following steps were performed on the other enantiomer (*S* configuration; this enantiomer has the shortest retention time).

The next step was deprotection to access enantiopure amino acids or close derivatives. To avoid racemization, the reaction conditions had to be very mild. After optimization, we succeeded in deprotecting compound (*S*)-**3b** in three steps under mild conditions (Scheme 2). Thus, basic hydrolysis of the oxazolidinone ring and subsequent esterification gave the corresponding methyl ester (*S*)-**4**. Formation of an ester was necessary to perform reduction of the amide with Schwartz's reagent,[15] which led to an imine that was hydrolyzed under acidic conditions.



Scheme 2. Deprotection of compound (*S*)-**3b** to give enantiopure amino ester (*S*)-**5**. TMS = trimethylsilyl, Cp = cyclopentadienyl.

Hence, we succeeded in the absolute asymmetric synthesis of enantiopure amino ester **5**. From a synthetic point of view, it is essential to know which enantiomer the synthetic sequence will give access to and thus to choose the initial crystal. Obviously, during the initial formation of small crystals of compound **1**, crystals of both enantiomers will be present at the same time in one flask. We envisaged that the sorting of these small crystals (a*R* and a*S*), if possible, would allow us to choose the desired enantiomer for the synthesis. Careful examination of the crystals did not show any notable differences, such as those observed by Pasteur in crystals of tartaric acid derivatives. Nevertheless, when we observed the small oriented crystals under polarized light,[16] we were able to sort the positive crystals, which induced light extinction when turned right, from the negative ones, which induced light extinction when turned left. Alkylation under the optimized conditions was repeated three times on crystals of each sign (on small crystals and once on a large crystal, after crystal growth) to give either enantiomer of compound **3b**. Analysis of compounds **3b** by HPLC using a chiral stationary phase confirmed that positive crystals gave access to the *R* enantiomer (as determined by crystallographic structure), and negative ones gave access to the opposite enantiomer. Thus, we have demonstrated that we are able to choose the appropriate crystal to obtain the desired enantiomer of compound **5**.

Concerning the stereoinduction of the reaction, it seems very likely that alkylation occurs opposite to the aromatic substituent. However, to prove this hypothesis, the absolute configuration (axial chirality around the Ar–CO bond) of the starting oxazolidinone **1** in the crystal still has to be determined. As the Flack parameter is not well-solved to provide an answer, vibrational circular dichroism[17] is under investigation to unravel this configuration. Preliminary results confirm the stereoinduction.

In conclusion, we demonstrated the successful absolute asymmetric synthesis of tertiary α-amino acid derivatives with high enantiomeric excesses, without using any chiral compound, but by using only frozen chirality of chiral crystals. The amino acid derivatives are obtained through a complex asymmetric two-step reaction (deprotonation and alkylation), during which the dynamic axial chirality is retained. The application of this work has allowed us to carry out the synthesis of an enantiopure α-amino ester. To our knowledge, this is the first example of the use of the frozen-chirality approach for the synthesis of biologically interesting compounds. Moreover, we have demonstrated that the frozen chirality of tertiary aromatic amides can efficiently serve as stereoinducer for alkylation. Finally, we are able to control the configuration of the final product by carefully sorting the initial crystals. We showed thus the usefulness of chiral crystals in organic reaction after sorting them under polarized light, crystal growth, and grinding with a planetary ball mill. Further development of this methodology, as well as proof of the stereoinduction, are under investigation.

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[1] Reviews: a) B. L. Feringa, R. A. van Delden, *Angew. Chem.* **1999**, *111*, 3624 – 3645; *Angew. Chem. Int. Ed.* **1999**, *38*, 3418 – 3438; b) I. Weissbuch, M. Lahav, *Chem. Rev.* **2011**, *111*, 3236 – 3267.

[2] a) P. de Marcellus, C. Meinert, M. Nuevo, J.-J. Filippi, G. Danger, D. Deboffle, L. Nahon, L. Le Sergeant d'Hendecourt, U. J. Meierhenrich, *Astrophys. J.* **2011**, *727*, L27; b) N. P. M. Huck, W. F. Jager, B. de Lange, B. L. Feringa, *Science* **1996**, *273*, 1686 – 1688; c) W. L. Noorduin, A. A. C. Bode, M. van der Meijden, H. Meekes, A. F. van Etteger, W. J. P. van Enckevort, P. C. M. Christianen, B. Kaptein, R. M. Kellogg, T. Rasing, E. Vlieg, *Nat. Chem.* **2009**, *1*, 729 – 732.

[3] N. Micali, H. Engelkamp, P. G. van Rhee, P. C. M. Christianen, L. Monsù Scolaro, J. C. Maan, *Nat. Chem.* **2012**, *4*, 201 – 207.

[4] W. L. Noorduin, E. Vlieg, R. M. Kellogg, B. Kaptein, *Angew. Chem.* **2009**, *121*, 9778 – 9784; *Angew. Chem. Int. Ed.* **2009**, *48*, 9600 – 9606.

[5] T. Matsuura, H. Koshima, *J. Photochem. Photobiol. C* **2005**, *6*, 7 – 24.

[6] A. Lennartson, S. Olsson, J. Sundberg, M. Håkansson, *Angew. Chem.* **2009**, *121*, 3183 – 3186; *Angew. Chem. Int. Ed.* **2009**, *48*, 3137 – 3140.

[7] O. Tissot, M. Gouygou, F. Dallemer, J.-C. Daran, G. G. A. Balavoine, *Angew. Chem.* **2001**, *113*, 1110 – 1112; *Angew. Chem. Int. Ed.* **2001**, *40*, 1076 – 1078.

[8] a) M. Sakamoto, *J. Photochem. Photobiol. C* **2006**, *7*, 183 – 196; b) F. Yagishita, M. Sakamoto, T. Mino, T. Fujita, *Org. Lett.* **2011**, *13*, 6168 – 6171.

[9] a) T. Kawasaki, T. Sasagawa, K. Shiozawa, M. Uchida, K. Suzuki, K. Soai, *Org. Lett.* **2011**, *13*, 2361 – 2363; b) I. Sato, K. Kadowaki, K. Soai, *Angew. Chem.* **2000**, *112*, 1570 – 1572; *Angew. Chem. Int. Ed.* **2000**, *39*, 1510 – 1512.

[10] a) M. Sakamoto, T. Iwamoto, N. Nono, M. Ando, W. Arai, T. Mino, T. Fujita, *J. Org. Chem.* **2003**, *68*, 942 – 946; b) M. Sakamoto, K. Fujita, F. Yagishita, A. Unosawa, T. Mino, T. Fujita, *Chem. Commun.* **2011**, *47*, 4267 – 4269; c) M. Sakamoto, A. Unosawa, S. Kobaru, K. Fujita, T. Mino, T. Fujita, *Chem. Commun.* **2007**, 3586 – 3588.

[11] a) M. Branca, S. Pena, D. Gori, R. Guillot, V. Alezra, C. Kouklovsky, *J. Am. Chem. Soc.* **2009**, *131*, 10711 – 10718; b) M. Branca, D. Gori, R. Guillot, V. Alezra, C. Kouklovsky, *J. Am. Chem. Soc.* **2008**, *130*, 5864 – 5865; c) M. Branca, V. Alezra, C. Kouklovsky, P. Archirel, *Tetrahedron* **2008**, *64*, 1743 – 1752; d) F. Bouillère, R. Guillot, C. Kouklovsky, V. Alezra, *Org. Biomol. Chem.* **2011**, *9*, 394 – 399; e) C. T. Hoang, F. Bouillère, S. Johannesen, A. Zulauf, C. Panel, D. Gori, A. Pouilhès, V. Alezra, C. Kouklovsky, *J. Org. Chem.* **2009**, *74*, 4177 – 4187; f) C. T. Hoang, V. Alezra, R. Guillot, C. Kouklovsky, *Org. Lett.* **2007**, *9*, 2521 – 2524.

[12] a) M. S. Betson, J. Clayden, M. Helliwell, P. Johnson, L. Wah Lai, J. H. Pink, C. C. Stimson, N. Vassiliou, N. Westlund, S. A. Yasin, L. H. Youssef, *Org. Biomol. Chem.* **2006**, *4*, 424 – 443; b) R. A. Bragg, J. Clayden, G. A. Morris, J. H. Pink, *Chem. Eur. J.* **2002**, *8*, 1279 – 1289; c) A. Ahmed, R. A. Bragg, J. Clayden, L. Wah Lai, C. McCarthy, J. H. Pink, N. Westlund, S. A. Yasin, *Tetrahedron* **1998**, *54*, 13277 – 13294.

[13] D. M. Bender, R. M. Williams, *J. Org. Chem.* **1997**, *62*, 6690 – 6691.

[14] L. Lecointe, V. Rolland, L. Papallardo, M. L. Roumestant, P. Viallefont, J. Martinez, *J. Peptide Res.* **2000**, *55*, 300 – 307.

[15] a) J. T. Spletstoser, J. M. White, A. Rao Tunoori, G. I. Georg, *J. Am. Chem. Soc.* **2007**, *129*, 3408 – 3419; b) D. J. A. Schedler, J. Li, B. Ganem, *J. Org. Chem.* **1996**, *61*, 4115 – 4119.

[16] T. Asahi, M. Nakamura, J. Kobayashi, F. Toda, H. Miyamoto, *J. Am. Chem. Soc.* **1997**, *119*, 3665 – 3669.

[17] L. A. Nafie, *Nat. Prod. Commun.* **2008**, *3*, 451 – 466.