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Tertiary Aromatic Amide for Memory of Chirality: Access to Enantioenriched α-Substituted Valine

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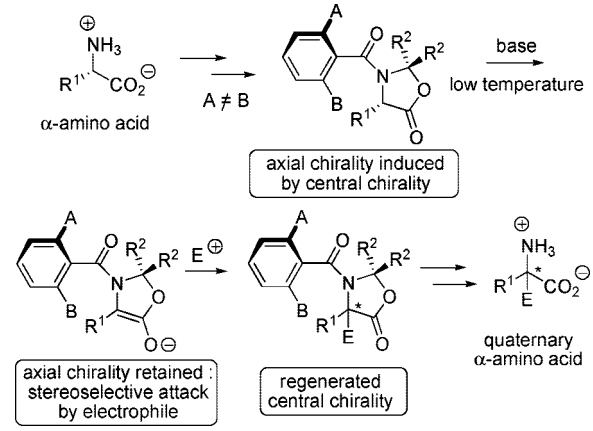
There is an ever-growing interest in the synthesis, pharmacology, and conformational properties of nonproteinogenic amino acids, and in particular α,α-disubstituted α-amino acids.[1] Due to their biological importance, many procedures have been developed for the stereoselective synthesis of quaternary α-amino acids.[2] Among them, some procedures apply a new principle, memory of chirality,[3,4] in order to use the starting α-amino acid as the only source of chirality. For instance, Fuji and Kawabata have performed essentially methylation and intramolecular alkylation of various α-amino acids with high enantiomeric excesses by using a nonracemic enolate with a chiral C−N axis.[5] Carlier used the intrinsic chirality of the benzodiazepine-2-one ring to obtain α,α-dialkyl amino acids enantioselectively.[6]

The high rotation barriers of tertiary aromatic amides have been exploited as a new method for diastereoselection.[7] We thought to apply the properties of these amides to the concept of memory of chirality, by introducing a hindered tertiary aromatic amide onto a starting amino acid. The generation of a dynamic axial chirality should allow stereoselective alkylation of the corresponding enolate after deprotonation (Scheme 1). For this purpose, N-substituted, amino acid derived, oxazolidin-5-ones were chosen as substrate for enantioselective alkylation. Herein, we report highly enantioselective synthesis of quaternary L-valine derivatives.

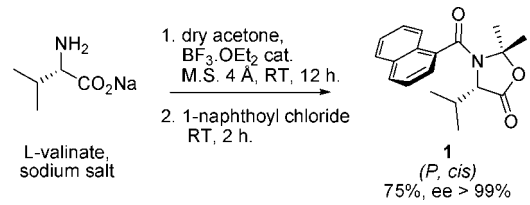
Compound **1** was selected and synthesized without racemization in one step from sodium L-valinate by modifying a procedure described by Seebach[8] (Scheme 2). The crystal structure of compound **1** indicated that, in the solid state, it adopts a (*P,cis*) conformation (Figure 1). This is consistent with the major conformation adopted in $CDCl_3$ at low temperature, according to our ^{1}H NMR and theoretical studies (*trans* conformers are destabilized by a decrease of conjugation in amide bond[9] and (*M,cis*) conformer by naphthyl distortion[10]).

We next attempted methylation of compound **1**. Deprotonation with KHMDS gave higher yields and enantioselectivities than with LDA. Additives, solvents, electrophiles, and reaction conditions (temperature, concentration, deprotonation time, or alkylation time) were then screened (Table 1). Increased enolate formation time improved yield but resulted in deterioration of the enantioselectivity. Yields and enantioselectivities generally increased when a cosolvent such as 1,2-dimethoxyethane (DME) was used. Using a crown ether dramatically boosted conversion but was deleterious to the enantiomeric excess (entry 5). Then, we replaced THF by the less polar diethyl ether. Conversion was, not surprisingly, slightly decreased, but racemization of the enolate was also slowed (entries 4 and 6). Good conversion was restored by replacing methyl iodide by the more reactive methyl triflate and increasing the concentration. Finally, the best conditions were the following: deprotonation with 1.5 equiv of KHMDS (in toluene) in diethyl ether/DME for less than 10 min and alkylation either with a very reactive electrophile for 10 min (entry 9) or with a less reactive electrophile with DMPU (entry 7). Lowering the temperature (−86 °C, entry 10) did not improve significantly the enantioselectivity, and increasing the temperature was deleterious (−60 °C, entry 11). Dissolution of crystals at −78 °C (entry 12) did not change enantioselectivity. These results suggested the formation of a dynamic chiral enolate, as expected.

Scheme 1. General Strategy to Enantioenriched Quaternary α-Amino Acids



Scheme 2. Synthesis of Compound **1**



We next applied the optimized conditions to other reactive electrophiles (Table 2): enantioselectivities exceed 73%, and yields range from 59 to 98%. Enantioselectivity can be enhanced by recrystallization for all compounds. Moreover, analysis of deuterated compound **2g** by chiral stationary-phase HPLC indicated retention of configuration.

Deprotection of compound **2a** (ee = 94%) or **2f** (ee > 99%) was achieved in one step: reflux in HBr 47% led quantitatively to

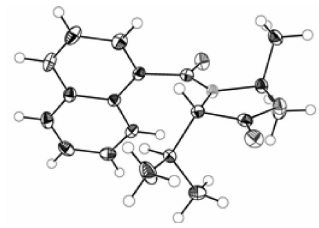


Figure 1. ORTEP plot of compound **1**. Ellipsoids are drawn at the 50% probability level.

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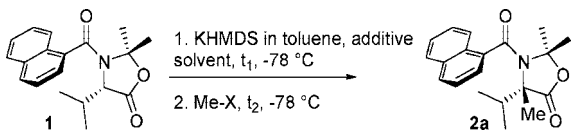
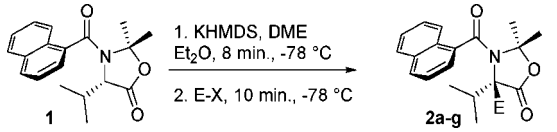
Table 1. Screening of Reaction Conditions for Methylation of Compound **1**[a]



entry	solvent	additive (equiv)	t_1 (min)	X (equiv)	t_2 (min)	conv (%)[b]	ee (%)[b]
1	THF		0[c]	I (6)	60	20	85
2	THF		4	I (30)	10	49	66
3	THF	DME (6)	4	I (30)	10	57	74
4	THF	DME (6)	10	I (30)	10	100	57
5	THF	18-c-6 (3)	1	I (30)	10	95	33
6	Et_2O	DME (6)	10	I (30)	10	87	79
7	Et_2O[d]	DME (3) DMPU (3)[e]	10	I (5)	10	88(74[f])	78
8	Et_2O[d]	DME (3)	3	OTf (3)	10	64	88
9	Et_2O[d]	DME (3)	8	OTf (5)	10	95(78[f])	82
10	Et_2O[d,g]	DME (3)	8	OTf (5)	10	93	85
11	Et_2O[d,h]	DME (3)	8	OTf (5)	10	99	54
12	Et_2O[d,i]	DME (3)	8	OTf (5)	10	82	83

[a] Unless specified, a mixture of KHMDS (3 equiv, 0.5 M in toluene) and additive was added via canula at −78 °C to a solution of **1**; concentration of enolate was 0.07 mol·L^{-1}. [b] Determined by chiral stationary-phase HPLC. [c] Electrophile in situ. [d] Only 1.5 equiv of KHMDS was added, and the concentration of the enolate was 0.15 mol·L^{-1}. [e] Added with electrophile. [f] Isolated yield. [g] Reaction at −86 °C. [h] Reaction at −60 °C. [i] Crystal dissolution at −78 °C.

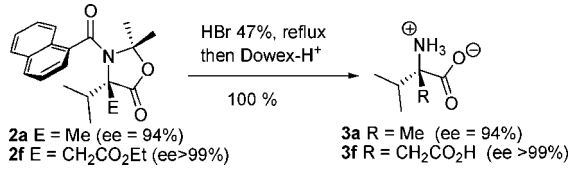
Table 2. Alkylation of Compound **1**



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

[a] Determined by chiral stationary-phase HPLC. [b] DMPU (3 equiv) added with MeI. [c] Complete conversion. [d] For unknown reasons, ee varies from 73 to 91%. [e] Percent deuteration determined by ^{1}H NMR spectroscopy.

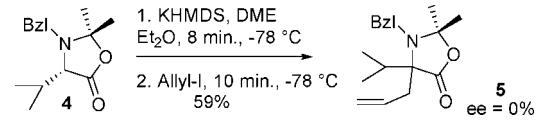
Scheme 3. Obtention of Enantioenriched α-Substituted Amino Acids



α-methyl valine **3a** or α-isopropyl aspartic acid **3f** (Scheme 3). The *S*-configuration was confirmed by comparison with optical rotation of known compounds.[11,12]

In order to confirm memory of chirality by dynamic axial chirality, we performed an alkylation reaction on compound **4**, using our optimized conditions. Only racemic product **5** was obtained in 59% yield (Scheme 4).

Scheme 4. Alkylation of Compound **4**



^{1}H NMR spectroscopy of **1** at 195 K in Et_2O/toluene demonstrates that the (*P,trans*) and (*M,trans*) conformers can be neglected and that a 100:12 ratio of (*P,cis*):(*M,cis*) conformers is observed. Since this ratio does not totally explain the conversion rates and enantioselectivities, we suggest that a dynamic resolution process also contributes to stereochemical induction: Ar−CO rotation in compound **1** 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 this enolate (Ar−CO rotation) should be relatively slow, and alkylation should occur opposite to the second aromatic ring, leading to global retention of configuration. Further NMR and theoretical studies are under investigation to confirm this hypothesis.

We have described herein a utilization of chiral Ar−CO axis of tertiary aromatic amides in the field of memory of chirality. Our methodology gives access to enantioenriched quaternary valine in only three steps. Future work will involve extension of this strategy to aldolization and to other amino acids.

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

References

(1) (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127–5143. (b) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537–4558.
(2) Recent reviews: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623. (b) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430.
(3) Reviews: (a) Fuji, K.; Kawabata, T. *Chem.—Eur. J.* **1998**, *4*, 373–376. (b) Kawabata T.; Fuji K. In *Topics in Stereochemistry*; Denmark, S. E., Ed.; John Wiley & Sons: New York, 2003; Vol. 23, pp 175−205. (c) Eames, J.; Suggate, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 186–189. (d) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1–16.
(4) Recent examples: (a) Kolaczkowski, L.; Barnes, D. M. *Org. Lett.* **2007**, *9*, 3029–3032. (b) Bonache, M. A.; Cativiela, C.; Garcia-Lopez, M. T.; Gonzalez-Muniz, R. *Tetrahedron Lett.* **2006**, *47*, 5883–5887.
(5) (a) Kawabata, T.; Chen, J.; Suzuki, H.; Fuji, K. *Synthesis* **2005**, 1368–1377. (b) Kawabata, T.; Kawakami, S.-p.; Shimada, S.; Fuji, K. *Tetrahedron* **2003**, *59*, 965–974. (c) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155–2157. (d) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153–4157.
(6) (a) Carlier, P. R.; Zhao, H.; MacQuarrie-Hunter, S. L.; DeGuzman, J. C.; Hsu, D. C. *J. Am. Chem. Soc.* **2006**, *128*, 15215–15220. (b) MacQuarrie-Hunter, S. L.; Carlier, P. R. *Org. Lett.* **2005**, *7*, 5305–5308. (c) Carlier, P. R.; Lam, P. C.-H.; DeGuzman, J. C.; Zhao, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2999–3002.
(7) (a) Betson, M. S.; Clayden, J.; Helliwell, M.; Johnson, P.; Lai, L. W.; Pink, J. H.; Stimson, C. C.; Vassiliou, N.; Westlund, N.; Yasin, S. A.; Youssef, L. H. *Org. Biomol. Chem.* **2006**, *4*, 424–443. (b) Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem.—Eur. J.* **2002**, *8*, 1279–1289. (c) Clayden, J.; Stimson, C. C.; Keenan, M. *Synlett* **2005**, 1716–1720.
(8) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243–1250.
(9) Branca, M.; Alezra, V.; Kouklovsky, C.; Archirel, P. *Tetrahedron* **2008**, *64*, 1743–1752.
(10) Unpublished results. Recent results indicate that the same major conformer is obtained with an alanine derived oxazolidinone.
(11) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A.; Lapena, Y. *Tetrahedron* **1995**, *51*, 5921–5928.
(12) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1987**, *28*, 2243–2246.

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