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Asymmetric α-Arylation of Amino Acid Derivatives by Clayden Rearrangement of Ester Enolates via Memory of Chirality

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Supporting Information

ABSTRACT: A method for asymmetric α-arylation of amino acid derivatives has been developed. The arylation was performed by Clayden rearrangement of ester enolates via memory of chirality to give hydantoins with an aryl-substituted tetrasubstituted carbon with up to 99% ee.

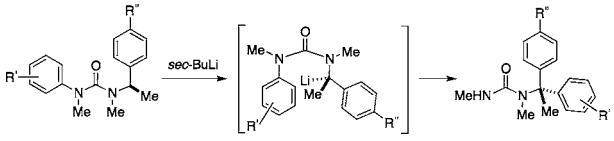
We have developed methods for asymmetric construction of α,α-disubstituted amino acid derivatives via memory of chirality (MOC).[1,2] Since the reactions take place via axially chiral enolate intermediates with limited half-lives of racemization, reactions of the chiral enolates with electrophiles compete with racemization of the chiral enolates themselves. Therefore, carefully controlled conditions are required for intermolecular alkylation,[3] conjugate addition,[4] and aldol reactions,[5] which must be performed at low temperatures (−78 to −60 °C) to minimize racemization of the intermediary chiral enolates. On the other hand, asymmetric intramolecular reactions via MOC can be performed at ambient or even higher temperature in the case where the intermediary chiral enolates can react immediately after they are generated.[6] Intramolecular alkylation,[6a,7] conjugate addition,[6b,c,8] and acyl migration[9] have been successfully developed. However, we have had difficulties in developing asymmetric α-arylation of amino acid derivatives even by employing the intramolecular protocol.[10] We have now focused on the intramolecular aryl migration process. Clayden and co-workers reported intramolecular electrophilic arylation of lithiated ureas.[11] Aryl groups on the nitrogen of the urea moiety were reported to migrate to the benzylic position with retention of configuration via an ipso S_NAr process (Scheme 1). This pioneering work on anionic aryl migration prompted us to develop an asymmetric arylation of chiral enolates derived from amino acid esters via MOC.[12−14]

The strategy for asymmetric α-arylation of amino acid derivatives is shown in Scheme 2. Treatment of *N*-MOM-*N*-C(=O)-substituted amino acid esters **I** (readily prepared from α-amino acids according to Clayden's protocol[11a]) with a base would generate axially chiral enolate **A** according to our protocol.[3−9] **A** would undergo intramolecular nucleophilic addition to the *N*-aryl group to give Meisenheimer-type complex **B**. Although the conversion of enolate **A** to anionic species **B** was expected to be difficult because the less stable (more basic) anionic species is to be generated, upon formation **B** would readily be transformed to the more stable urea anion **C**. To facilitate the transformation of **A** into **B**, we initiated the study using **I** with R^1 = *p*-NO_2 (**2**).

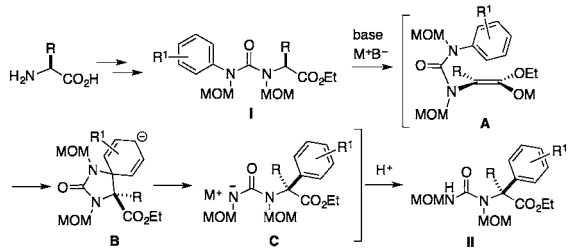
The preparation of urea **2** is shown in Scheme 3. Condensation of the HCl salt of L-phenylalanine ethyl ester with *p*-nitrophenyl isocyanate gave urea **1** in 91% yield. Introduction of a methoxymethyl (MOM) group onto the anilinic NH group under acidic conditions followed by introduction of the second MOM group onto the NH group of the phenylalanine moiety under basic conditions gave **2** in 65% yield without racemization. According to our previous studies, the MOM group on the nitrogen of the amino acid moiety in **2** was assumed to be critical for the generation of the axially chiral enolate with high enantiomeric purity.

Asymmetric migration of the enolate generated from **2** was examined (Table 1). We previously found that a base system [potassium hexamethyldisilazide (KHMDS) in dimethylformamide/tetrahydrofuran (DMF/THF) at −60 °C] is suitable for highly enantioselective intramolecular alkylation of chiral

Scheme 1. Clayden's Anionic Aryl Migration



Scheme 2. Strategy for Asymmetric Aryl Migration of Chiral Enolates via Memory of Chirality



Scheme 3. Preparation of Urea Derivative 2

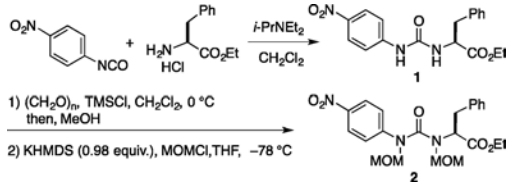


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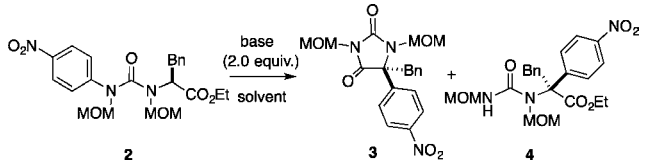
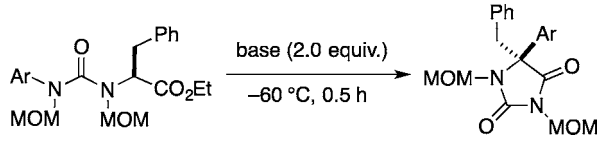
Table 1. Asymmetric Aryl Migration of Phenylalanine–Urea Derivative 2[a]



entry	base, solvent	T (°C), t (h)	% yield (% ee[b]) of **3**	% yield of **4**
1	KHMDS, 3:2 DMF/THF	−60, 0.5	93 (83)	–
2	NaHMDS, 8:1 DMF/THF	−60, 0.5	64 (93)	24
3	LiHMDS, 4:1 DMF/THF	−60, 0.5	59 (99)	15
4	LiHMDS, 4:1 DMF/THF	−60 to 15, 0.5	68 (97)	–
5	KHMDS, THF	−78, 0.5	80 (7)	8
6	NaHMDS, THF	−78, 0.5	62 (73)	20
7	LiHMDS, THF	−78, 0.5	18 (−23[c])	–
8	KHMDS, toluene	0, 0.5	55 (−25[c])	42
9	NaHMDS, toluene	0, 0.5	51 (−83[c])	29
10	NaHMDS, toluene	−78, 3.5	62 (−61[c])	26
11	LiHMDS, toluene	0, 1	37 (−74[c])	11

[a]The reactions were run at a substrate concentration of 0.1 M under an Ar atmosphere. [b]Absolute configurations were tentatively assigned by analogy to **22**, **24**, and **26**. [c]**3** was obtained with the absolute configuration opposite to that in entries 1–6.

Table 2. Scope of Aryl Groups in Asymmetric Aryl Migration of Phenylalanine–Urea Derivative[a]



entry	substrate: Ar	base,[b] solvent	product:[c] % yield (% ee)
1[d]	**2**: 4-$NO_2C_6H_4$	LiHMDS, 4:1 DMF/THF	**3**: 68 (97)
2	**5**: 4-CNC_6H_4	LiHMDS, 5:1 DMF/THF	**6**: 90 (98)
3	**7**: 4-BrC_6H_4	LiHMDS, 5:1 DMF/THF	**8**: 97 (95)
4[e]	**9**: 4-$MeOC_6H_4$	KHMDS, 1:1 DMF/THF	**10**: 0[f] (–)
5	**11**: 1-naphthyl	LiHMDS, 5:1 DMF/THF	**12**: 47 (84)
6	**13**: C_6H_5	KHMDS, 3:2 DMF/THF	**14**: 73[g] (55)
7	**15**:[h] C_6H_5	KHMDS, 1:1 DMF/THF	**16**: 46[i] (73)

[a]Reactions were run at a substrate concentration of 0.1 M. [b]Both LiHMDS and KHMDS were examined for each substrate. Only the conditions that gave the product with the higher ee are shown. [c]Absolute configurations were tentatively assigned by analogy to **22**, **24**, and **26**. [d]The reaction was run at −60 to 15 °C. [e]Run for 24 h. [f]The substrate was recovered. [g]The substrate was recovered in 37% yield. [h]Substrate **15** had an *N*,*N*-diphenyl group (no *N*-MOM group). [i]The substrate was recovered in 40% yield.

enolates generated from amino acid esters.[7–9] Treatment of **2** with 2.0 equiv of KHMDS in 3:2 DMF/THF at −60 °C for 0.5 h gave hydantoin **3** as the sole product (93% yield) with 83% ee (entry 1).

Hydantoin **3** was expected to form by intramolecular acylation of the in situ-generated N-anion of **4**. Use of NaHMDS gave **3** in 64% yield with 93% ee and **4** in 24% yield (entry 2). While the use of LiHMDS gave **3** with a further-improved 99% ee, the yield of **3** was diminished to 59% (entry 3). Raising the temperature from −60 to 15 °C afforded **3** as the sole product in 68% yield with 97% ee (entry 4). This indicates that the anion of **4** is the initial product in the formation of **3**. The use of THF as the solvent resulted in a decrease in the enantioselectivity (entries 5–7). The reactions of **2** in toluene at elevated temperature (0 °C) gave **3** with the absolute configuration opposite to that obtained by the reactions in DMF/THF (entries 8, 9, and 11). The reaction of **2** with NaHMDS in toluene at 0 °C gave **3** with higher enantioselectivity (83% ee) than obtained at −78 °C (61% ee) (entry 9 vs 10). Similar solvent and temperature effects were observed in enantiodivergent cyclization of amino acid esters via MOC.[7b,15]

Asymmetric α-arylation of *N*-aryl-*N*-MOM-phenylalanine–urea derivatives with various aryl groups was also examined (Table 2). The reactions of urea derivatives possessing an *N*-aryl group substituted with an electron-withdrawing group proceeded with high enantioselectivity (95–98% ee; entries 1–3). 4-Cyanophenyl and 4-bromophenyl derivatives **5** and **7** gave α-arylated hydantoins **6** and **8** with 98% ee (90% yield) and 95% ee (97% yield), respectively (entries 2 and 3). The aryl migration was not observed in substrate **9** with an electron-donating aryl group (4-OMe-C_6H_4) (entry 4). To our surprise, anionic aryl migration was also observed in substrates **11**, **13**, and **15** with unactivated aryl groups (entries 5–7). The reaction of *N*-(1-naphthyl)urea derivative **11** with LiHMDS gave α-arylated hydantoin **12** with 84% ee in 47% yield (entry 5). While asymmetric aryl migration proceeded even in *N*-phenylurea derivative **13** to give α-phenylhydantoin **14** with a moderate 55% ee, the corresponding reaction of the *N*,*N*-diphenyl derivative **15** gave the product with an improved 73% ee (entries 6 and 7).

The asymmetric aryl migration was further examined using various *N*-aryl-*N*-MOM-urea derivatives derived from L-valine and L-methionine (Table 3). 4-Bromophenyl- and 4-nitrophenyl derivatives derived from L-methionine, **17** and **19**, underwent asymmetric aryl migration with high enatioselectivity upon treatment with LiHMDS in DMF/THF at −60 °C to give α-arylated hydantoins **18** and **20** with 96% ee (86% yield) and 96% ee (71% yield), respectively (entries 1 and 2). Asymmetric aryl migration in 4-bromophenyl derivative **21** derived from L-valine upon treatment with LiHMDS afforded hydantoin **22** with 99% ee (25% yield) and the initial arylated product before cyclization in 66% yield (entry 3). The corresponding reaction at higher temperature (−60 to 20 °C) gave hydantoin **22** as the sole product in 80% yield with 98% ee (entry 4). The use of KHMDS instead of LiHMDS at −60 °C gave hydantoin **22** in quantitative yield but with a moderate 56% ee (entry 5). α-Arylated hydantoin **24** was obtained with high enantioselectivity (99% ee) in quantitative yield upon treatment of 4-nitrophenyl derivative **23** derived from L-valine with LiHMDS at −60 to 20 °C (entry 6). The corresponding *N*-phenyl derivative **25** gave α-arylated hydantoin **26** with 61% ee in 86% yield (entry 7). The absolute configuration of **26** was determined to be *S* by its conversion and comparison with known (*R*)-**27**.[16] The absolute configuration of hydantoins **22** and **24** were also determined to be *S* by their chemical correlation to (*R*)-**27** [see the Supporting Information (SI)]. Thus, asymmetric aryl migration in **21**, **23**, and **25** was found to proceed with inversion of configuration.

The behavior of the intermediary chiral enolates toward racemization was investigated (Scheme 4). We previously determined the barrier to racemization of the axially chiral

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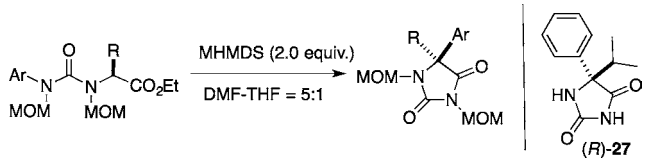
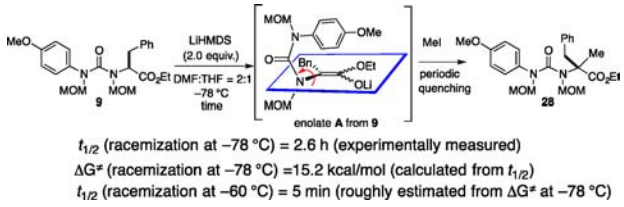
Table 3. Asymmetric Aryl Migration in Various Urea Derivatives Derived from L-Valine and L-Methionine[a]



entry	substrate: R	Ar	M	T (°C), t (h)	product: % yield (% ee)
1	**17**: $MeS(CH_2)_2$	$4\text{-}BrC_6H_4$	Li	−60, 0.5	**18**:[b] 86 (96)
2	**19**: $MeS(CH_2)_2$	$4\text{-}NO_2C_6H_4$	Li	−60, 0.5	**20**:[b] 71 (96)
3	**21**: *i*-Pr	$4\text{-}BrC_6H_4$	Li	−60, 0.5	**22**:[c] 25[d] (99)
4	**21**: *i*-Pr	$4\text{-}BrC_6H_4$	Li	−60 to 20, 0.5−12[e]	**22**:[c] 80 (98)
5	**21**: *i*-Pr	$4\text{-}BrC_6H_4$	K	−60, 0.5	**22**:[c] 99 (56)
6	**23**: *i*-Pr	$4\text{-}NO_2C_6H_4$	Li	−60 to 20, 0.5−12[e]	**24**:[c] 99 (99)
7	**25**: *i*-Pr	C_6H_5	K	−60, 3	**26**:[c] 86 (61)

[a]Reactions were run at a substrate concentration of 0.1 M. [b]Absolute configurations were tentatively assigned by analogy to **22**, **24**, and **26**. [c]*S* isomer. [d]The α-arylated product before cyclization was obtained in 66% yield. [e]After being stirred for 30 min at −60 °C, the mixture was gradually warmed to 20 °C over a period of 12 h.

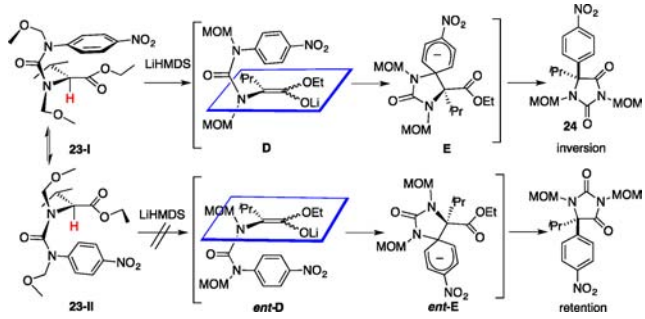
Scheme 4. Racemization Behavior of Chiral Enolate A Derived from 9



enolate generated from an *N*-MOM-*N*-Boc-L-phenylalanine derivative by periodic quenching of the chiral enolate with methyl iodide.[1b,3,6a] However, this protocol could not be applied to the enolates generated from the present substrates because they underwent aryl migration immediately after they were generated. We chose to use compound **9** to estimate the racemization barrier of the chiral enolate because enolate **A** (Scheme 2) generated from **9** was expected not to undergo aryl migration (Table 2, entry 4). The barrier to racemization of lithium enolate **A** generated from **9** in 2:1 DMF/THF at −78 °C was determined through the periodic quenching of the enolate with methyl iodide (Scheme 4; for details, see the SI). The barrier was found to be 15.2 kcal/mol at −78 °C. The half-life of racemization of the chiral enolate at −60 °C (the reaction temperature) was roughly estimated to be 5 min from the racemization barrier at −78 °C on the basis of the assumption that $\Delta S^{\ddagger} \approx 0$ for the unimolecular racemization process (bond rotation along the chiral C−N axis).

A rationale for the stereochemical course of the asymmetric aryl migration of **23** is shown in Scheme 5. A conformational search of **23** gave the stable conformers **23-I** and **23-II**.[17] Deprotonation of **23-I** with LiHMDS, where the C(α)−H (shown in red) bond is antiperiplanar with respect to the neighboring N−(C═O)N(MOM)Ar bond, would be preferable to that of **23-II**, where the C(α)−H (shown in red) bond is antiperiplanar with respect to the neighboring N−C(MOM) bond. This was assumed on the basis of our previous stereochemical results, in which deprotonation of *N*-Boc-*N*-alkyl-α-amino acid derivatives preferentially took place from the conformer in which the C(α)−H bond is antiperiplanar with respect to the N−C(Boc) bond.[1b,3−9] Deprotonation of conformer **23-I** would give enantiomerically enriched enolate **D**, which would undergo intramolecular addition to the

Scheme 5. A Possible Stereochemical Course for Asymmetric Aryl Migration



neighboring *N*-aryl group to give Meisenheimer-type complex **E**. Collapse of **E** followed by intramolecular N-acylation would give α-arylated hydantoin **24** with inversion of configuration.

In conclusion, we have developed a method for asymmetric α-arylation of amino acid derivatives. The reaction involves Clayden rearrangement of chiral enolates generated from α-amino acid esters via the protocol of MOC. This method provides chiral hydantoins with an aryl-substituted tetrasubstituted carbon, which are potentially useful chiral building blocks in the field of medicinal chemistry[18] and are structural equivalents to amino acids with aryl-substituted tetrasubstituted carbons.[19]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews of asymmetric synthesis via MOC, see: (a) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1. (b) Kawabata, T. *ACS Symp. Ser.* **2009**, *1009*, 31. For the first report of MOC, see: (c) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

(2) For recent reports on related asymmetric reactions via axially chiral enolates, see: (a) Ghorai, M. K.; Ghosh, K.; Yadav, A. K.; Nanaji, Y.; Halder, S.; Sayyad, M. *J. Org. Chem.* **2013**, *78*, 2311. (b) Mai, T. T.; Viswambharan, B.; Gori, D.; Kouklovsky, C.; Alezra, V. *J. Org. Chem.* **2012**, *77*, 8797. (c) Fletcher, S. P.; Solá, J.; Holt, D.; Brown, R. A.; Clayden, J. *Beilstein. J. Org. Chem.* **2011**, *7*, 1304. (d) Branca, M.; Pena, S.; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711. (e) Kolaczkowski, L.; Barnes, D. M. *Org. Lett.* **2007**, *9*, 3029. (f) MacQuarrie-Hunter, S.; Carlier, P. R. *Org. Lett.* **2005**, *7*, 5305. (g) Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 11482. (h) Gerona-Navarro, G.; Bonache, M. A.; Hernz, R.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2001**, *66*, 3538.

(3) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155.

(4) Yoshimura, T.; Kinoshita, T.; Yoshioka, H.; Kawabata, T. *Org. Lett.* **2013**, *15*, 864.

(5) Watanabe, H.; Yoshimura, T.; Kawakami, S.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Chem. Commun.* **2012**, *48*, 5346.

(6) (a) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153. (b) Yoshimura, T.; Takuwa, M.; Tomohara, K.; Uyama, M.; Hayashi, K.; Yang, P.; Hyakutake, R.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Chem.—Eur. J.* **2012**, *18*, 15330. (c) Monguchi, D.; Yoshimura, T.; Irie, K.; Hayashi, K.; Majumdar, S.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Heterocycles* **2012**, *86*, 1483.

(7) (a) Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012. (b) Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. *J. Am. Chem. Soc.* **2006**, *128*, 15394. (c) Yoshimura, T.; Tomohara, K.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 7102.

(8) Kawabata, T.; Majumdar, S.; Tsubaki, K.; Monguchi, D. *Org. Biomol. Chem.* **2005**, *3*, 1609.

(9) Teraoka, F.; Fuji, K.; Ozturk, O.; Yoshimura, T.; Kawabata, T. *Synlett* **2011**, 543.

(10) Attempted intramolecular Pd-catalyzed asymmetric α-arylation reactions of chiral enolates derived from α-amino acid esters resulted in low asymmetric induction (up to 32% ee) because of significant racemization of the chiral enolates during the reactions (data not shown). Pd-catalyzed arylation reactions of enolates were performed at rt to 90 °C employing the methods shown in ref 14.

(11) (a) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. For related carbanionic aryl migrations, see: (b) Clayden, J.; Famaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hiller, I. H.; Vincent, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 3410. (c) Clayden, J.; Donnard, J.; Lefranc, J.; Minassi, A.; Tetlow, D. *J. Am. Chem. Soc.* **2010**, *132*, 6624. (d) Fournier, A. M.; Clayden, J. *Org. Lett.* **2012**, *14*, 142. (e) Tetlow, D. J.; Vincent, M. A.; Hiller, I. H.; Clayden, J. *Chem. Commun.* **2013**, *49*, 1548. (f) Tait, M.; Donnard, M.; Minassi, A.; Lefranc, J.; Bechi, B.; Carbone, G.; O'Brien, P.; Clayden, J. *Org. Lett.* **2013**, *15*, 34.

(12) For asymmetric arylation of amino acid derivatives by asymmetric aryl rearrangement of aryl sulfonamides, see: (a) Lupi, V.; Penso, M.; Foschi, F.; Gassa, F.; Mihali, V.; Tagliabue, A. *Chem. Commun.* **2009**, 5012. (b) Foschi, F.; Landini, D.; Lupi, V.; Mihali, V.; Penso, M.; Pilati, T.; Tagliabue, A. *Chem.—Eur. J.* **2010**, *16*, 10667.

(13) For chiral-auxiliary-based asymmetric α-arylation of amino acid derivatives, see: (a) Tayama, E.; Kimura, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 8869. (b) Makosza, M.; Sulikowski, D.; Maltsev, O. *Synlett* **2008**, 1711. (c) Tayama, E.; Orihara, K.; Kimura, H. *Org. Biomol. Chem.* **2008**, *6*, 3673. (d) Sulikowski, D.; Makosza, M. *Eur. J. Org. Chem.* **2010**, 4218. (e) Jones, E. P.; Jones, P.; White, A. J. P.; Barrett, A. G. M. *Beilstein J. Org. Chem.* **2011**, *7*, 1570. (f) Jones, E. P.; Jones, P.; Barrett, A. M. G. *Org. Lett.* **2011**, *13*, 1012.

(14) For pioneering reports on racemic synthesis of α-arylated amino acid derivatives via Pd-catalyzed arylation of enolates, see: (a) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. (b) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465. (c) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, *5*, 1915. (d) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *11*, 1549.

(15) A possible explanation for the solvent dependence is as follows: Deprotonation of **23-I** (Scheme 5) is basically preferable to give enantiomerically enriched enolate **D** followed by the product with inversion of configuration. Deprotonation of **23-II** seems to be preferential only in less-coordinative solvents such as toluene because coordination of the countercation of the base with the urea carbonyl group would become crucial in a less-coordinative solvent and would give chiral enolate ***ent*-D** followed by the product with retention of configuration.

(16) Coquerel, G.; Petit, S. *J. Cryst. Growth* **1993**, *130*, 173.

(17) A conformational search for **23** was performed by a molecular modeling search (MCMM, 10 000 steps) with the OPLS 2005 force field using MacroModel (v. 9.0). Conformer **23-I** was suggested to be 1.2 kcal/mol less stable than the most stable conformer **23-II**. For details, see the SI.

(18) For example, see: Stilz, H. U.; Guba, W.; Jablonka, B.; Just, M.; Klingler, O.; König, W.; Wehner, V.; Zoller, G. *J. Med. Chem.* **2001**, *44*, 1158.

(19) Amino acid derivatives with an aryl-substituted tetrasubstituted carbon are a new type of chiral building blocks for drug discovery. For example, see: Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Tepe, J. J. *Bioorg. Med. Chem.* **2009**, *17*, 3093.