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"Extreme" Ugi Reactions With Some Complex α-Amino Acids

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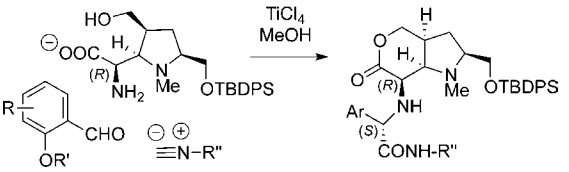
ABSTRACT



The Ti(IV)-catalyzed Ugi condensation of α-amino acids with electron-rich aromatic aldehydes performs adequately even with sterically demanding α-amino carboxylate salts. The reaction occurs diastereoselectively, in some cases with virtually complete diastereoselectivity. A stereochemical rationale for the reaction is proposed.

A need to alleviate at least some of the difficulties encountered in the Ugi reaction of α-amino acids[1] with aromatic aldehydes, especially electron-rich ones, induced us to devise a Ti(IV)-catalyzed variant of the process that significantly improved kinetics and yields.[2] Recently, an opportunity arose to test the limits of this chemistry with complex α-amino acids **1**–**2** as substrates (Figure 1). The Ugi reaction of **1**–**2** piqued our interest because the NH_2 group in either molecule is hindered, and its nucleophilic character is inductively attenuated by the neighboring NMe unit. Moreover, the free acid forms of **1**–**2** lactonize easily. It will be seen shortly that the corresponding lactones are not substrates for the Ugi reaction, while the open forms are. The open structure of the substrates can only be preserved by formation of a carboxylate salt, which therefore would have to be employed as such in the Ugi step. However, this would deprive the medium of protonic catalysis, hampering the overall process by retarding the rate of imine formation (an acid-catalyzed process). The problem would be especially acute with less electrophilic aromatic aldehydes bearing electron-releasing substituents. A successful condensation of a carboxylate salt of **1**–**2** with an electron-rich aromatic aldehyde and an isonitrile would thus constitute an "extreme" Ugi reaction, the feasibility of which may seem doubtful.

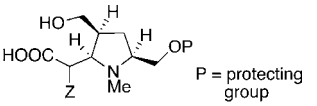


Figure 1. Structure of α-amino acids **1** and **2**.

Compounds **1** and **2** are required for an ongoing project in total synthesis[3] and may be reached from the known lactone **3** (Scheme 1),[4] starting with *N*-methylation to **4**. The direct azidation[5] of the enolate of **4** was problematic, but iodination proceeded efficiently to furnish **5** as a single diastereomer[6] and in nearly quantitative yield. The configuration of **5**, which segues from an approach of the electrophilic agent from the convex face of the enolate, was ascertained by the presence of dipolar coupling (NOE) between H_a and the NMe hydrogens.[7] Iodide **5** underwent facile nucleophilic substitution with azide ion.

(1) Reviews: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) De Graaf, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969.

(2) Godet, T.; Bonvin, Y.; Vincent, G.; Ciufolini, M. A. *Org. Lett.* **2004**, *6*, 3281.

(3) Turner, C. D. Dissertation; University of Bristish Columbia, 2012.

(4) Turner, C. D.; Ciufolini, M. A. *Heterocycles* **2012**, *85*, 85.

(5) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(6) Within the limits of 300 MHz ^{1}H NMR.

(7) Coupling constants were of little use in this case. For instance, in **5** the value of $^3J_{ab}$, 1.4 Hz disallowed an unequivocal assignment.

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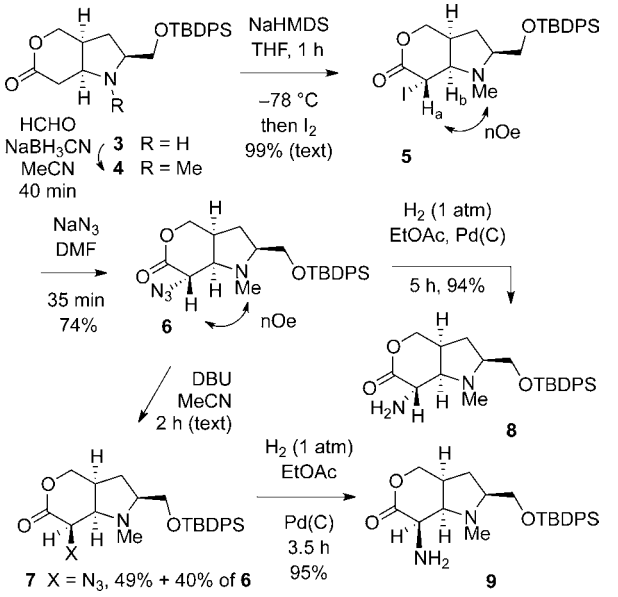
Scheme 1. Preparation of Diastereomeric Aminolactones **8** and **9**

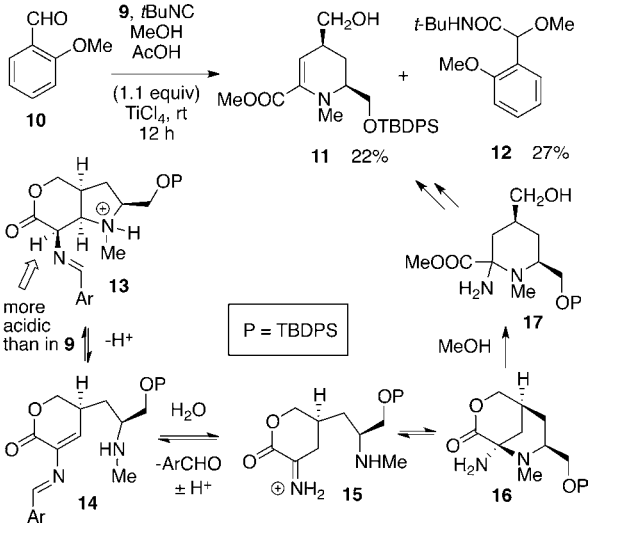


However, product **6** was formed as the α-azido diastereomer, as apparent again from an NOE correlation between H_a and the NMe hydrogens. Lactone **7** was thus a product of nucleophilic substitution of I^- with retention of configuration, indicating that either the NMe unit had anchimerically assisted the departure of the nucleofuge or epimerization at the C=O α-position had occurred at some point during the reaction. In the interest of evaluating the ease of epimerization of the azidolactones, substance **6** was treated with DBU in MeCN. This resulted in equilibration to a 1.2:1 mixture of epimeric lactones **7** (major) and starting **6** (minor). Evidently, the two epimers of the α-azido-lactone are nearly isoenergetic, indicating that the conversion of **5** into **6** cannot be attributed to equilibration after the substitution event, and implying that in all likelihood the nucleophilic displacement of iodide had occurred with anchimeric assistance. Lactones **6** and **7** were readily separated by SiO_2 flash chromatography, and each was uneventfully hydrogenated to furnish α-amino-lactones **8** and **9**, the configuration of which was ultimately confirmed by an X-ray structure of a derivative (*vide infra*).

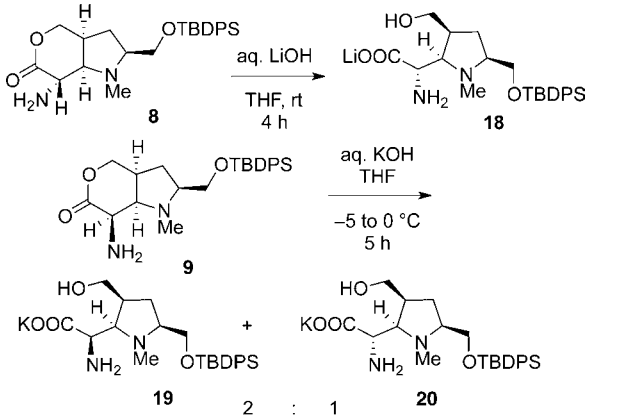
As indicated earlier, the lactones are incompetent Ugi substrates. In this respect, attempted condensation of **9** with *o*-anisaldehyde, **10**, and *t*-Bu-NC resulted in formation of tetrahydropyridine **11** (22%) plus Passerini-type amide **12** (27%)[8] as the sole identifiable products (Scheme 2). A brief investigation of the unanticipated reaction leading to **11** revealed that the aldehyde is required,[9] even though it is not incorporated into the final product. An explanation might be that **9** and **10** must first combine to afford imine **13**, wherein the increased acidity of the carbonyl α-proton, and the stabilization of the incipient **14** by conjugation with the aromatic ring, promote *β*-elimination of the pyrrolidine

(8) For a reaction leading to products similar to **12**, see ref 2.
(9) In the absence of the aldehyde, only slow decomposition occurs.

Scheme 2. Attempted Ugi Reaction with Lactone **9**



Scheme 3. Saponification of Aminolactones **8** and **9**



nitrogen. The aldehyde is no longer needed at this point: it is released from **14**, and the resulting **15** advances to **11**.

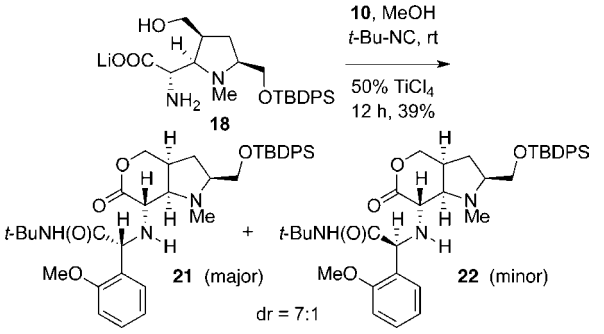
The saponification of aminolactone **8** occurred smoothly in the presence of aqueous LiOH to afford salt **18**. By contrast, the hydrolysis of **9** took place with a variable degree of epimerization at the α-center. This undesirable effect could be contained by carrying out the reaction with aqueous KOH at 0 °C, whereupon a 2:1 mixture of salts **19** (major) and **20** resulted (Scheme 3; notice that compound **20** is the K^+ carboxylate version of **18**). Separation of the very polar isomeric salts was best avoided, and subsequent experiments were carried out with mixture of the two.

Unsurprisingly, the Ugi reactions of **18**–**19** with electron-rich aromatic aldehydes required more than the customary 5 mol % of Ti(IV). Still, reactions run at a 50 mol % catalyst load returned the expected Ugi products in moderate yield.[10] Salt **18** combined with *o*-anisaldehyde and *t*-BuNC

(10) No reaction took place in the absence of $TiCl_4$.

to afford a 7:1 mixture of products that were epimeric at the level of the newly formed stereogenic center (39% from **8**). These were tentatively (*vide infra*) assigned as **21** (major) and **22** (Scheme 4). No effort was made to further improve these reactions, which afforded only lactone-type products: evidently, the internal primary alcohol, instead external MeOH, had intercepted a transient imino ester intermediate.[11] Also, the experiment described in Scheme 2 implies that **21**–**22** arise from an open form of the substrate, and not from lactone **8**.

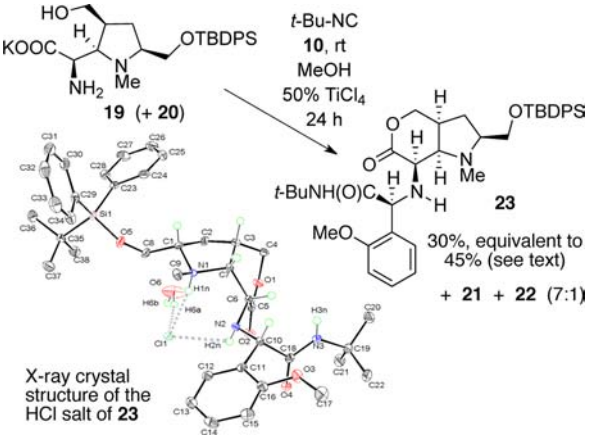
Scheme 4. Ugi Reaction of Carboxylate Salt **18**



The reaction of salt **19** (contaminated with ca. 33% of **20**) proceeded in a similar fashion. However, product **23** (30% yield from **9**, corresponding to 45% based on the molar fraction of **19** in the starting mixture of salts) was obtained substantially as a single diastereomer,[6] while contaminant **20** advanced to the anticipated 7:1 mixture of **21** and **22** (Scheme 5). Silica gel flash chromatography readily achieved separation of **23** from its isomers. The HCl salt of **23** deposited diffraction quality crystals that enabled an X-ray structural determination.[12] This revealed that the newly formed stereocenter had the (*S*)-configuration (cf. ORTEP plot in Scheme 5).

It seems appropriate to venture a rationale for the stereochemical course of the above reaction, especially since the literature provides no consistent picture for similar transformations.[1] Diastereoselectivity is probably determined by an irreversible attack of the isonitrile onto the more favorable *E*-isomer of the imine arising upon condensation of the amino acid with the aldehyde. The isonitrile could possibly add to a chelate complex of the imine (Figure 2). This may be tenable in the present case, given the amount of $TiCl_4$ present in the medium. However, such a model implies that the reaction of, e.g., an α-(*S*)-amino acid (i.e., an L-amino acid) should *always* lead to a product in which the newly formed stereocenter is of *R*-configuration or, at the very least least, that the Lewis acid should have an influence on the diastereomeric ratio of the products. This is not the case.[2] We believe instead that the isonitrile adds to the more accessible face of

Scheme 5. Ugi Reaction of Carboxylate Salt **19**



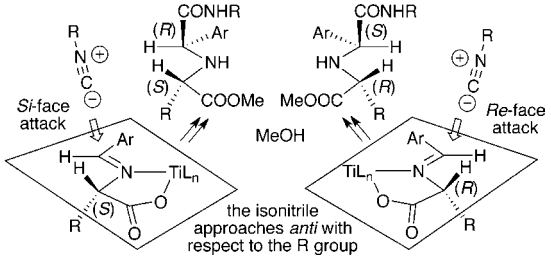


Figure 2. Possible chelated model for Ti-catalyzed Ugi reaction.

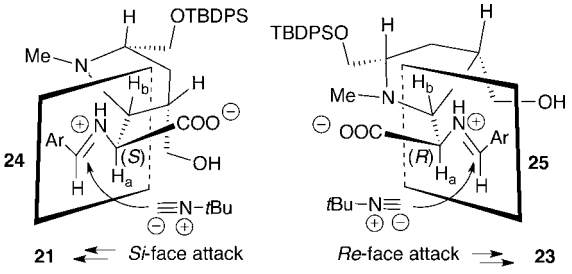


Figure 3. Nonchelated model for Ti-catalyzed Ugi reactions.

iminium ions **24**–**25** (Figure 3). An MM+ study[13] of closely related species[14] revealed a preference for a conformation in which the carboxylate unit is approximately normal (±9°) to the plane of the imino linkage and H-α and H-*β* are nearly *anti*. In α-(*S*) amino acid derived **24**, the NMe moiety thus hinders access to the *Re*-face to a greater degree that the $COO^{(-)}$ group hampers access to the *Si*-face. Reaction from the *Si*-face is thus preferred.

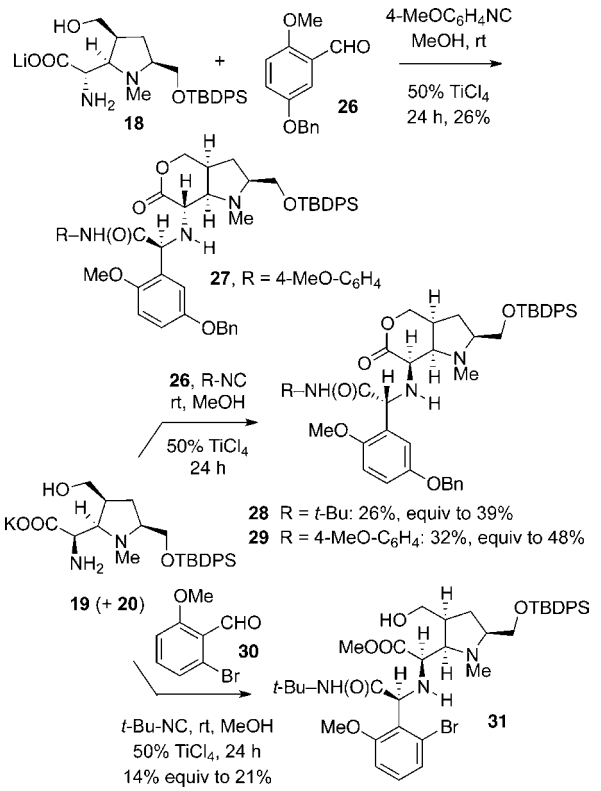
(11) Compare: Ugi, I.; Demharter, A.; Hörl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657.

(12) By contrast, various salts of **21** have yet to crystallize in a form suitable for an X-ray diffractometric study.

(13) Calculations were carried out with the Hyperchem package, available from Hypercube, Inc., Gainesville, FL.

(14) Details are provided as Supporting Information.

Scheme 6. Ugi Reactions with Aldehydes **26** and **30**



Conversely, in the iminium ion derived from the α-(*R*) amino acid, it is the CH−CH_2OH branch that blocks access to the *Si*-face, promoting reaction from the *Re*-face.[15] Interestingly, a similar analysis leads to accurate predictions regarding the sense of stereoselectivity of other Ugi reactions of α-amino acids recorded in the literature.[16] On the basis of this model and of the X-ray structure of **23**, we tentatively assign the configuration of Ugi products **21**−**22**, as well as **27**−**29** and **31** (Scheme 6), as shown herein, pending confirmation by X-ray diffractometry.

Further experiments indicated that aldehydes carrying additional substitution on the aromatic nucleus react normally, so long as they are not 2,6-disubstituted. For instance, the reaction of aldehyde **26** with 4-MeO-C_6H_4-NC and salt **18** produced **27** as the major component of an 8.5:1 mixture of diastereomers (26% overall yield from **8**), while an analogous reaction with **19** (contaminated with about 33% of **20**) and *tert*-Bu-NC or 4-MeO-C_6H_4-NC afforded **28** (26% from **9**, equivalent to 39% when corrected for the molar fraction of **19** in the mixture of salts) and **29** (32% from **9**, equivalent to 48%), respectively (Scheme 6; only the products derived from **19**, essentially single diastereomers,[6] are shown). However, the reaction of aldehyde **30** with **19**−**20** was inefficient (14%, equivalent to 21%). This is attributable to further steric retardation of the rate of both imine formation and of nucleophilic attack thereon, due to the 2,6-disubstituted nature of the aldehyde. It is worth noting that product **31** was obtained as a methyl ester, and not as a lactone.[17]

In conclusion, the Ti(IV)-catalyzed Ugi reaction of α-amino acids with aromatic aldehydes performs adequately even with complex, hindered, carboxylate salts such as **18**−**19**, so long as the aldehyde is not 2,6-disubstituted. In the latter case, slower rates of imine formation and of nucleophilic attack of the isonitrile depress overall yields to synthetically unattractive levels. Ugi products thus obtained may be valuable building blocks for the assembly of certain alkaloidal frameworks.[3,18] Research aiming to optimize these transformations and to explore their synthetic potential is ongoing. Pertinent results will be disclosed in due course.

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Supporting Information Available. Experimental procedures and characterization data for new compounds, plus ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) One may infer from the *A*-value of an NMe_2 vs that of a $CHMe_2$ (1.53 kcal/mol vs 2.52 kcal/mol: Eliel, E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994; pp 696−697) that the steric demand of a CH−CH_2OH branch is greater than that of an NMe unit. Therefore, a CH−CH_2OH should provide more effective steric shielding of one of the imine faces than an NMe; i.e., it should promote higher diastereoselectivity. This is consistent with observation.

(16) Details will be provided in a forthcoming full paper.

(17) In addition to the expected **21**−**23**, **27**−**29**, and **31**, the Ugi reactions described herein returned mixtures of numerous uncharacterized products. No evidence was ever garnered for the presence of starting lactones **8**−**9** or tetrahydropyridine **11** in such mixtures.

(18) For instance, those found in the quinocarcin/bioxalomycin/cyanocyclin family of cytotoxic natural products: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

The authors declare no competing financial interest.