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Chiral Pyrroline-Based Ugi-Three-Component Reactions Are under Kinetic Control

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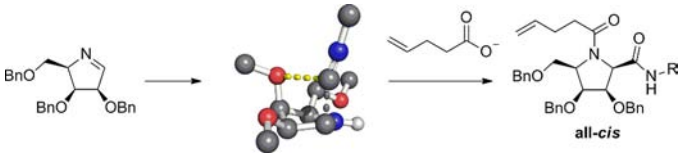
ABSTRACT



Although it is often assumed that the stereochemistry in Ugi multicomponent reactions is determined in the final Mumm rearrangement step, experimental and computational evidence that Ugi reactions on hydroxylated pyrrolines proceed under kinetic control is reported. The stereochemistry of the reaction is established with the addition of the isocyanide to the intermediate iminium ion, whose conformation is determined by its substitution pattern.

The Ugi reaction is one of the most widely used multicomponent reactions and has found extensive application in the generation of structural diversity in diverse compound libraries.[1] In the classic Ugi four-component reaction, an aldehyde, an amine, a carboxylic acid, and an isocyanide are combined to form a diamide motif. In this event, the aldehyde is condensed with the amine to generate an imine (**3**, Scheme 1a). This species is protonated by the carboxylic acid component to provide an iminium ion (**4**), which is attacked by the isocyanide to generate a nitrilium ion (**5**). This cation is intercepted by the carboxylate to form an intermediate imidate (**6**). Mumm rearrangement of this imidate leads to the final Ugi product (**7**).[2] In the closely related Ugi-three-component reaction, preformed imines are made to react with an isocyanide and a carboxylic acid. As a result of an Ugi multicomponent reaction, a new chiral center is formed between the two newly created amide functions and it is often assumed that the stereoselectivity in the reaction is determined by the irreversible Mumm rearrangement, which terminates the series of preceding equilibria.[1−3]

In the past few years we explored the use of chiral, carbohydrate-derived azidoaldehydes (exemplified by pentose-derived 4-azido-aldehyde **8**) to generate cyclic imines as a starting point for an ensuing Ugi three-component reaction process (see Scheme 1b).[4,5] During the course of these investigations we observed that some of these reactions proceeded with excellent stereoselectivity while

(1) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234.

(2) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153.

(3) Ugi, I.; Meyr, R. *Chem. Ber.* **1961**, *94*, 2229.

(4) (a) Timmer, M. S. M.; Risseeuw, M. D. P.; Verdoes, M.; Filippov, D. V.; Plaisier, J. R.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *Tetrahedron: Asymmetry* **2005**, *16*, 177. (b) Bonger, K. M.; Wennekes, T.; Filippov, D. V.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2008**, 3678. Wennekes, T.; Bonger, K. M.; Vogel, K.; van den Berg, R. J. B. H. N.; Strijland, A.; Donker-Koopman, W. E.; Aerts, J. M. F. G.; van der Marel, G. A.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2012**, 6420.

(5) Bonger, K. M.; Wennekes, T.; de Lavoir, S. V. P.; Esposito, D.; van den Berg, R. J. B. H. N.; Litjens, R. E. J. N.; van der Marel, G. A. *QSAR Comb. Sci.* **2006**, *25*, 491.

(6) For related studies, see: (a) Chapman, T. M.; Davies, I. G.; Gu, B.; Block, T. M.; Scopes, D. I. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. A.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2005**, *127*, 506. (b) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 6637. (c) Banfi, L.; Basso, A.; Guanti, G.; Merlo, S.; Repetto, C.; Riva, R. *Tetrahedron* **2008**, *64*, 1114. (d) Cerulli, V.; Banfi, L.; Basso, A.; Rocca, V.; Riva, R. *Org. Biomol. Chem.* **2012**, *10*, 1255. (e) Flanagan, D. M.; Joullié, M. M. *Synth. Commun.* **1989**, *19*, 1. (f) Bowers, M. M.; Carroll, P.; Joullié, M. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 857.

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Scheme 1. (a) Ugi Multicomponent Reaction; (b) Ugi Reaction on a Preformed Pyrroline, Generated from a D-Pentose Derived 4-Azido Aldehyde, through a Staudinger-aza-Wittig Reaction

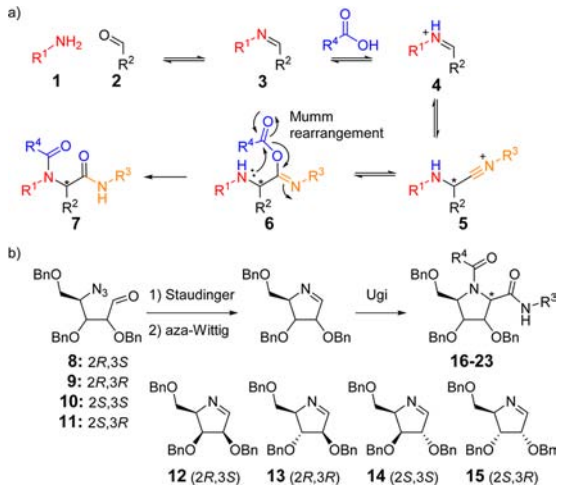


Table 1. Products of the Ugi Reaction on D-Pentose Derived Pyrrolines **12**–**15**[a]

azido-aldehyde	imine	Ugi product	R =	R =
			2,3-*cis*:2,3-*trans*	2,3-*cis*:2,3-*trans*
8	**12**		55% >98:2 **(16a) (16b)**	60% >98:2 **(17a) (17b)**
9	**13**		50% 58:42 **(18a) (18b)**	61% 54:46 **(19a) (19b)**
10	**14**		39% 43:57 **(20a) (20b)**	37% 45:55 **(21a) (21b)**
11	**15**		49% >98:2 **(22a) (22b)**	51% >98:2 **(23a) (23a)**

[a] Reaction conditions: (1) PMe_3, MeOH, 0 °C; (2) pent-4-enoic acid, RNC, MeOH, 0 °C.[10]

others provided diastereomeric products with little or no selectivity.[6,7] For example, the D-*lyxo* configured pyrroline (**12**) gave after Ugi reaction with a variety of isocyanides and carboxylates exclusively the all-*cis* substituted pyrrolidines, whereas the D-*arabino* configured pyrroline (**13**) provided the 2,3-*cis*- and 2,3-*trans*-products in almost equal amounts.[5,8] The stereochemical course of these reactions is obviously guided by the configuration of the starting imine, but is not easily explained by considering the Mumm rearrangement as the stereoselectivity determining step. Would this be true, then formation of the thermodynamically more stable product would be expected. Here we describe experimental and computational studies on the Ugi three-component reaction of all four possible 4-deoxy-4-azido-D-pentose derived pyrrolines **12**–**15**. Our results indicate that the stereoselectivity of these Ugi multicomponent reactions is based on kinetic control and is determined at the stage of attack of the isocyanide at the iminium ion.

The four diastereomeric pentose-derived azidoaldehydes used in this study, **8** (D-*lyxo*), **9** (D-*arabino*), **10** (D-*xylo*), and **11** (D-*ribo*), and corresponding imines (**12**–**15**) are depicted in Scheme 1b. Table 1 shows the results of the Ugi reaction using these imines with either *tert*-butylisocyanide or cyclohexylisocyanide and pent-4-enoic acid.[9] To fully ascertain the stereochemistry of the newly formed stereocenters in products **16**–**23**, the pentenoyl groups, which give rise to rotameric product mixtures, were removed by iodine mediated hydrolysis (see Table S1, Supporting Information). The structures of the resulting products were unambiguously established with ^1H and ^{13}C NMR spectroscopy.[9]

The Ugi three-component reaction on *lyxo*-configured imine **12** proceeded with excellent 2,3-*cis*-stereoselectivity to provide the all-*cis*-linked pyrrolidines **16a** and **17a**, in line with our previous observations. A similar stereochemical outcome is observed for the *ribo*-configured imine **15**, with only the 2,3-*cis* pyrrolidines **22a** and **23a** formed. In contrast, Ugi three-component reaction on the *arabino*- and *xylo*-configured imines (**13** and **14**) proceeded with virtually no stereoselectivity.

We argue that the stereochemical outcome of the Ugi reaction cannot be rationalized through appreciation of the steric interactions in the products **16**–**23**. For example, unfavorable 2,3-*cis* interactions would already be manifest in the imidate intermediates (**6**), thereby eliminating the Mumm rearrangement as the step governing the stereochemical outcome of the reaction. Rather, we were drawn to the parallels between the stereochemical course of *C*-allylation reactions on furanosyl oxocarbenium ions as reported by Woerpel and co-workers[11] and the stereochemical outcome of our Ugi three-component reactions. Woerpel and coworkers proposed a model to account for the stereoselectivity observed in *C*-allylation reactions of furanosides based on the conformational preferences of the intermediate oxocarbenium ions. They reasoned that the orientational preferences of the ring substituents dictate the relative stabilities of the possible oxocarbenium ion envelope conformers. Alkoxy substituents at C-2 and C-3 (oxocarbenium ion numbering) preferentially take up an equatorial and axial position, respectively (as in **25b**, see Scheme 2). The C-4 alkyl

(7) Chiral precursors have been shown to direct stereoselectivity: (a) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587.

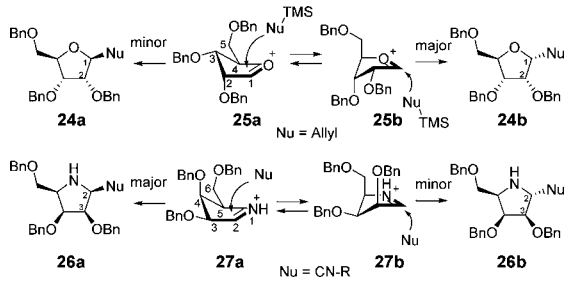
(8) In this paper pyrrolidine numbering is used.

(9) See Supporting Information for the synthesis of the starting azidoaldehydes, the full experimental details on the reaction conditions, analytical data, energy diagrams, and optimized structures of the calculations.

(10) Product ratios are determined by ^1H NMR at 393 K to allow free rotation around the newly formed tertiary amide bond.

(11) (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879. (b) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149.

Scheme 2. D-*Ribose* Oxocarbenium Conformers **25a** and **25b** Attacked by Allyltrimethylsilane and D-*Lyxo* Configured Iminium Ion Conformers **27a** and **27b** Attacked by an Isocyanide



substituent (oxocarbenium ion numbering) does not have a strong preference for either orientation but can play an important role in combination with the other ring substituents through mutual steric interactions. Nucleophiles would then approach the intermediate envelope oxocarbenium ions preferentially from the "inside" (the side of the envelope *syn* to the carbon atom which lies out of the envelope plane) to avoid developing eclipsing interactions with the neighboring ring substituent. A final contributing factor they identified was the steric interaction between the substituents and the incoming nucleophile. When these conformational preferences are translated to the iminium ions at hand it becomes clear that the D-*lyxo* iminium ion preferentially adopts an ^4E-conformation (**27a** Scheme 2, iminium ion numbering), allowing the C-3 and C-4 substituents to take up a preferred orientation. Inside attack on this iminium ion leads to the all-*cis*-product. In the same vein, the D-*ribo* iminium ion prefers the E_4-envelope and inside attack on this conformer accounts for the formation of the 2,3-*cis* products. For the D-*arabino* and the D-*xylo* iminium ions the substituent preferences are conflicting, resulting in a mixture of iminium ion conformers of comparable stability and thereby leading to a mixture of diastereomeric products.

To gain more insight into the course of the Ugi reactions on pentose derived pyrrolines, we performed a quantum-mechanical DFT study[12,9] in which we calculated the relative energies of the intermediates through which the reaction passes for all four diastereomeric imines, starting from either envelope conformer. The calculations were performed at the B3LYP/6-31G* level with inclusion of the solvent (methanol) through a Polarized Continuum Model and employed methyl substituted imines, methyl isocyanide, and acetic acid as reaction partners.[13] Energies of the individual reactants were added to the energies of the protonated imines and the nitrilium species in order to compare relative energies. In addition, transition states were calculated for the attack of the isocyanide on the protonated imines.[9]

Scheme 3 (top) shows the reaction pathway energy diagram of the D-*lyxo* configured imine **12** starting at the protonated imine (**27**). The pathway shows two exothermic steps, one, the formation of the imidate (**28**) from the nitrilium ion (**27**) and, the other, the Mumm rearrangement, proceeding through a cyclic intermediate[14] (**30**) that is higher in energy than the preceding imidate.[15] The large drop in energy in going from the nitrilium ion to the imidate indicates that the addition of the carboxylate to the nitrilium ion is essentially nonreversible. Therefore the stereochemistry of the Ugi reaction is determined before this event. The calculations provide support for the two-conformer hypothesis, described above. Thus, two low energy conformations were found for the D-*lyxo* iminium ion (**27a** and **27b**), of which the ^4E-envelope ion (**27a**) is the one lower in energy. This conformer places the C-3 and C-4 substituents in favorable positions while steric interactions between the C-3 and C-5 substituent are minimal in this structure. Notably, the difference in energies between the conformers is larger in the two transition states (**28a** and **28b**) in which the isocyanide attacks the iminium ions than in the starting envelope conformers **27a** and **27b**. This contrasts the perception that steric interactions between the axially oriented C-4 substituent and the incoming nucleophile make transition state **28a** less favorable. A close inspection of transition state **28a** for the attack on the methyl isocyanide on the ^4E iminium ion reveals that the C-4 substituent actually approaches the incoming nucleophile. A possible explanation for this approach is the electrostatic stabilization of the positive charge that develops on the isocyanide carbon atom by the C-4 oxygen substituent while the addition progresses.[16] Scheme 3 (bottom) depicts the course of the addition and shows the $^4E \rightarrow {}^4T_3 \rightarrow E_3$ reaction trajectory in which the stabilizing interaction of the C-4-substituent and the incoming nucleophile becomes clear. The calculated difference in energy between the two transition states ($\Delta\Delta E^{\ddagger}$ = 2.5 kcal mol^{-1}; 2,3-*cis*/2,3-*trans*, **28a**/**28b** = 98:2) corroborates the observed stereoselectivity in the Ugi reaction of imine **12** (experimental 2,3-*cis*/2,3-*trans* = >98:2).

The other three imine stereoisomers show similar energy diagrams,[9] indicating that the reaction pathways of the Ugi reactions of these imines are comparable to the one described for the D-*lyxo* imine.[17] The relative energies of the iminium ion envelope conformers, the transition states of the corresponding isocyanide additions, and the resulting nitrilium ions are listed in Table 2. Although the overall

(12) For similar theoretical approaches, see: (a) Maeda, S.; Komagawa, S.; Uchiyama, M.; Morokuma, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 644. (b) Chéron, N.; Ramozzi, R.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, *77*, 1361.

(13) The stereoselectivity of the Ugi reaction of the per-*O*-methylated *xylo* derived imine was similar to that for the Ugi reaction of its per-*O*-benzylated counterpart (see Supporting Information).

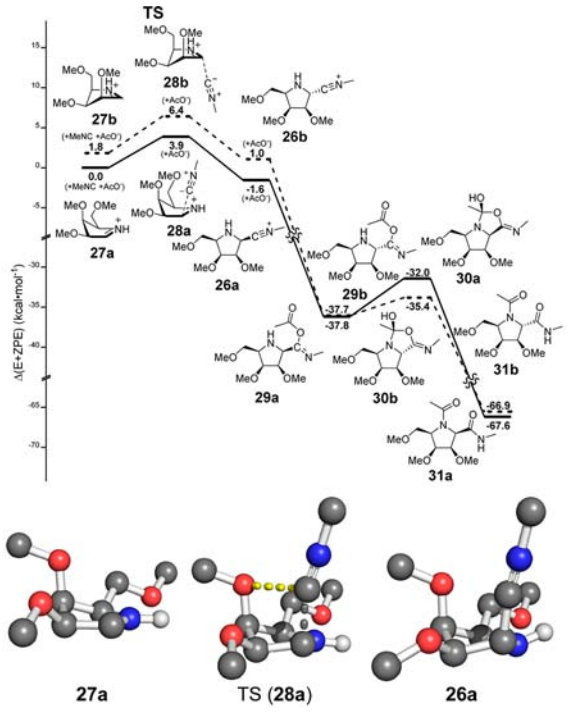
(14) Several bicyclic intermediates can be formed in this reaction step, differing in the stereochemistry of the newly formed hemiaminal linkage and the stereochemistry of the double bond (see Supporting Information). The lowest energy intermediate is shown in the figure.

(15) Although the addition of the isocyanide to the imine can also be envisioned to proceed via an S_N2-like pathway in which the incoming isocyanide displaces an anomeric (covalent) acetate, we deem this pathway to be less likely given the stabilities of the intermediate iminium ions and the polarity of the solvent.

(16) Chao, C. S.; Lin, C. Y.; Mulani, S.; Hung, W. C.; Mong, K. K. T. *Chem.—Eur. J.* **2011**, *17*, 12193.

(17) When all iminium ions are compared it becomes clear that the ^4E *Ara* is the most stable conformer of the four isomers (^4E *Lyxo* = 1.00 kcal mol^{-1}, ^4E *Ara* = 0.00 kcal mol^{-1}, E_4 *Xylo* = 0.96 kcal mol^{-1}, E_4 *Ribo* = 0.99 kcal mol^{-1}).

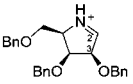
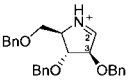
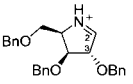
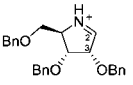
Scheme 3. (Top) Energy Diagram of the Ugi Reaction on the D-*Lyxo* Configured Imine Starting at the Iminium Ion;[a] (Bottom) Optimized Structures of the D-*Lyxo* ^4E Iminium Ion (**27a**), the Transition State (**28a**) of the Attack of the Isocyanide on This Ion, and the Resulting Nitrilium Ion (**26a**)



[a] Energies are given relative to the combined energy of the ^4E iminium ion **27a** and its reaction partners.

reaction pathways are similar there are important differences to note. For both the D-*arabino* and D-*xylo* configured iminium ions, the energy difference between the transition states of the isocyanide additions is smaller than the difference in energy between the starting envelope conformers. Also here the stabilizing interaction of the axially oriented C4-substituent with the nucleophile becomes apparent. For example, while the D-*xylo* configured E_4 iminium ion is favored over its ^4E counterpart by 1 kcal mol^{-1}, the transition state originating from the latter ion is slightly lower in energy than the transition state derived from the former. The D-*ribo* Ugi reaction energy profile parallels that of its D-*lyxo* congener. The difference in energy between the two isocyanide addition transition states is larger than the energy difference between the parent iminium ion envelopes leading to the selective formation of the 2,3-*cis*-nitrilium ion and subsequently the 2,3-*cis*-Ugi product. The calculated energy differences between the transition states nicely match the experimental stereoselectivities for the four diastereomeric imines as summarized in Table 2. Finally, the calculations confirm that the relative stabilities of the Ugi products cannot account for the observed selectivities.[9]

Table 2. Relative Energies of Iminium Ion Conformers, Transition States, Nitrilium Ions, and Theoretical Product Ratios

starting iminium ions	products	iminium ions (kcal mol^{-1})	TSs (kcal mol^{-1})	nitrilium ions (kcal mol^{-1})
Lyxo 	2,3-*cis* (**16a**)	E_4: 0.0	E_4: 3.9	-1.6
	2,3-*trans* (**16b**)	^4E: 1.8	^4E: 5.4	1.0
			$\Delta\Delta E^{\ddagger}$ = 2.5	(**16a**:**16b** = 98:2)
Arabino 	2,3-*cis* (**18a**)	^4E: 0.0	^4E: 4.4	-1.0
	2,3-*trans* (**18b**)	E_4: 1.3	E_4: 4.5	-0.9
			$\Delta\Delta E^{\ddagger}$ = -0.1	(**18a**:**18b** = 55:45)
Xylo 	2,3-*cis* (**20a**)	E_4: 0.0	E_4: 4.4	-1.6
	2,3-*trans* (**20b**)	^4E: 1.0	^4E: 4.3	-1.8
			$\Delta\Delta E^{\ddagger}$ = 0.1	(**20a**:**20b** = 45:55)
Ribo 	2,3-*cis* (**22a**)	E$_4$: 0.0	E$_4$: 4.4	-1.8
	2,3-*trans* (**22b**)	^{4}E: 1.1	^{4}E: 5.8	-0.3
			$\Delta\Delta E^{\ddagger}$ = 1.4	(**22a**:**22b** = 91:9)

In conclusion, our experimental results supported by the calculational data reported here show that the diastereoselectivity of the Ugi three-component reaction using pentose derived pyrrolines is determined in the transition state of the isocyanide addition step to the iminium ion and that these reactions therefore proceed under kinetic control. This stands in contrast to the classic mechanistic view that the Ugi reaction proceeds through a series of equilibrium reactions before ending with the irreversible Mumm rearrangement in the thermodynamically favored product. For the pyrrolines studied here, the conformation of the iminium ion intermediates, in combination with the stabilizing effect of an axially positioned C-4 ether on the developing positive charge in the incoming nucleophile, is the deciding factor in the stereochemical course of the isocyanide addition reaction. It might well be that the kinetic scenario described here is not only valid for the pyrrolines used in this study but also of importance for many other Ugi reactions and other multicomponent reaction featuring isocyanides. Our results therefore may help in the development of predictive models for diastereoselective Ugi-type multicomponent reactions, which would have considerable impact in library design for drug discovery and development.

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Supporting Information Available. Experimental details, calculational and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.