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FULL PAPER

DFT Studies on the Stereoselective Three-Component Ugi Reaction

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Abstract:

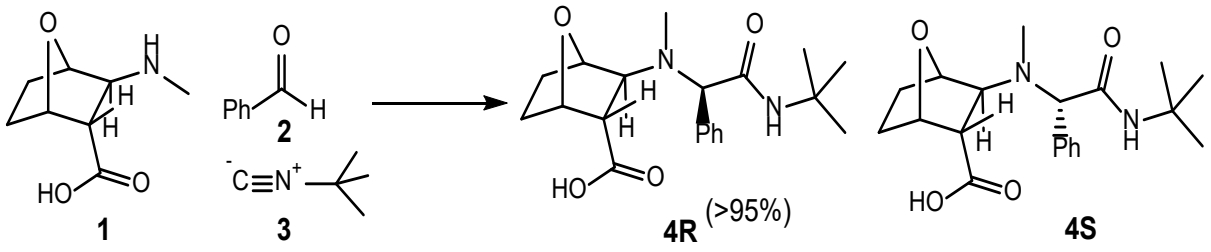
Mechanism and stereochemistry of three component Ugi reaction (3C-Ugi) were studied theoretically based on DFT calculations. Structures of reagents, products, intermediates, and transition states were optimized at M062X/6-31+g(d,p) level of theory in gas phase and in methanol as a common solvent for this reaction. The reaction takes place through several processes, including atom inversion, bond rotation, acid-base, nucleophile-electrophile competitions. These diverse phenomena were studied to provide a clearer picture of the mechanism of this valuable reaction, especially in terms of stereochemistry considerations. According to the results, the enthalpy of the reaction was -45.9 and -41.2 kcal/mol for the dominant product in gas phase and in methanol. The stereoselectivity of the reaction was under the kinetic control of nucleophilic attack of isocyanide to less hindered si-face (E_a= 4.1 compared to 7.4 kcal/mol for re-face) of more stable chiral (E)-iminium in methanol.

Keywords: DFT calculation; multicomponent reaction; stereoselectivity; three-component Ugi reaction

1. Introduction

Multicomponent reactions (MCRs) are processes in which three or more reagents are reacted in one pot to form one product. Three component Ugi reaction is one of the most studied and famous MCRs, which consists of condensation of an amine, an aldehyde and an isocyanide to form an aminoamide derivative [1-3]. Several mechanistic studies and explanations have been made by Ugi and others since 1959 [4]. The most reliable representation involved an iminium that is trapped by an isocyanide to give the resulting aminoamide [5, 6].

The products of 3C-Ugi reaction are aminoamide derivatives that their stereochemistry play an outstanding role in protein and other biochemical sciences. Several attempts have been made to improve stereoselectivity utilizing chiral isocyanides and chiral cyclic imines [7-13]. Stereoselectivity was improved significantly in the presence of chiral amines. In one successful example, the utilizing of chiral amine (**1**) in 3C-Ugi reaction had induced high diastereoselectivity to the formation of aminoamide derivatives (**4R**:**4S**, >95%) (Scheme 1) [14].



Scheme 1. Diastereoselective 3C-Ugi reaction.

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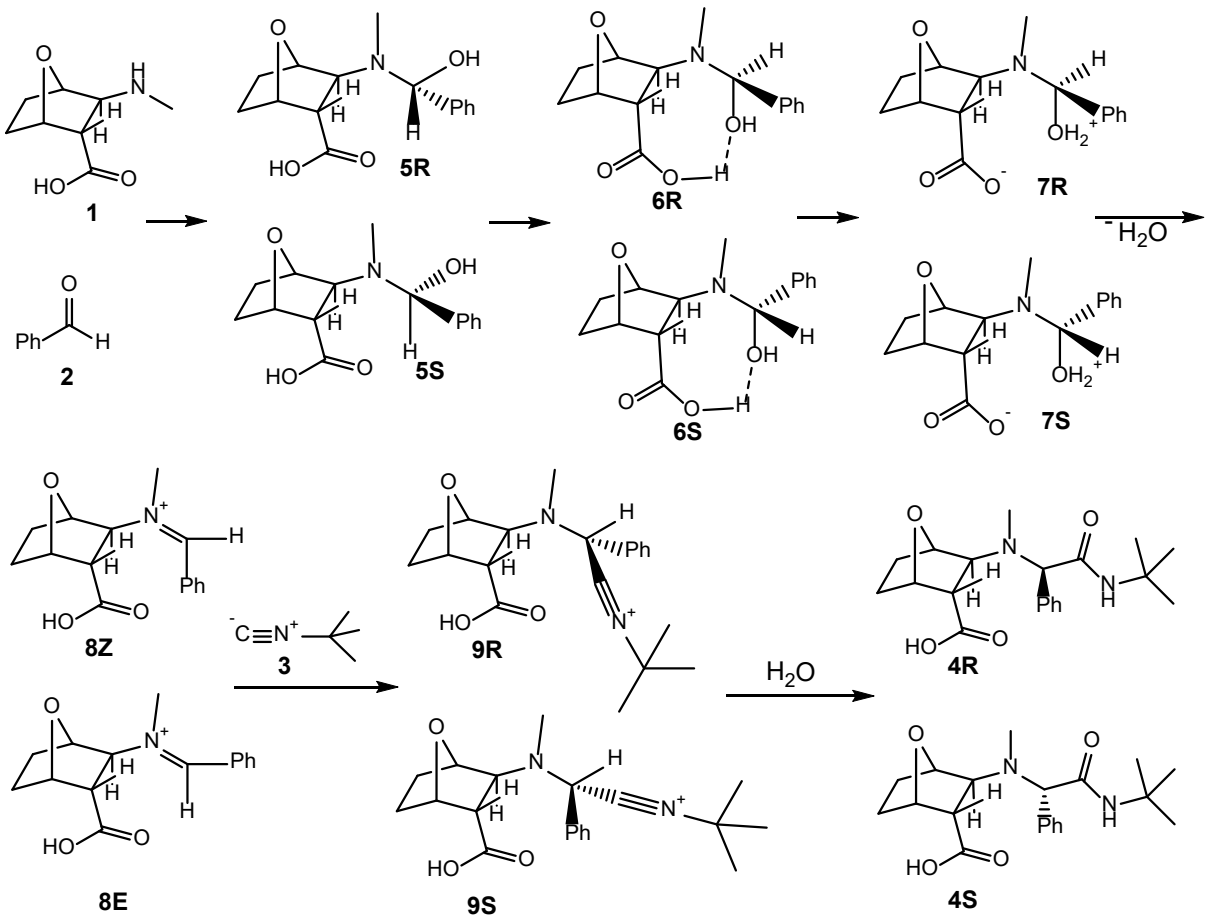
Although there are lots of data for three component Ugi reaction (3C-Ugi) and its mechanism, based on our literature survey there were not sufficient theoretical studies concerning explanation of the stereoselectivity of 3C-Ugi reaction. Recently we reported DFT studies on the diastereoselectivity of four-component Ugi reaction in which, diastereoselectivity of the reaction was under kinetic and thermodynamic controls of nucleophilic attack of isocyanide to less hindered re-face of chiral (E)-iminium ion [15]. Increasing interests in theoretical calculations on multi-component reaction, coupled with serious insufficient information concerning prediction of the stereochemistry of this reaction was the impetus to study mechanism and stereoselectivity of 3C-Ugi reaction in the present study [16, 17]. We would like to present theoretically how to predict and explain the outcome of stereoselectivity and kinetic or thermodynamic control of 3C-Ugi reaction in the presence of a chiral amine.

2. Results and Discussion

According to the reliable proposal mechanism outline of 3C-Ugi reaction, there are lots of possibilities and phenomena including amine inversions, proton transfers, isomerizations, and nucleophile-electrophile interactions and competitions (Scheme 2). In the first step, chiral amine (**1**) reacts with aldehyde (**2**) to produce hemiaminal (**5**). Intramoleculare proton transfer converts **5** to intermediate **7** via conformer **6**. Intermediate **7** is dehydrated to yield iminium ion **8** as E- and Z-isomers. Isocyanide (**3**) attacks to re-face and si-face of 8E and **8Z** and produces intermediate nitrilium ion **9R** and **9S** having one more stereocenter. Finally, hydrolysis of **9** leads to the formation of aminoamides **4R** and **4S**.



Scheme 2. Mechanism of distereoselective 3C-Ugi reaction.

To study the mechanism of the reaction, ground states of reagents, relative stabilities of

isomers and components involved in the mechanism of 3C-Ugi reaction were optimized in gas phase by DFT calculations at M062X/6-31+g(d,p) level of theory and the results for 3 starting materials (**1**-**3**), 14 intermediates and transition states (**5**-**9**) and two products (**4**) were summarized in Table 1. The Cartesian coordinates of optimized structures were presented in supporting file.

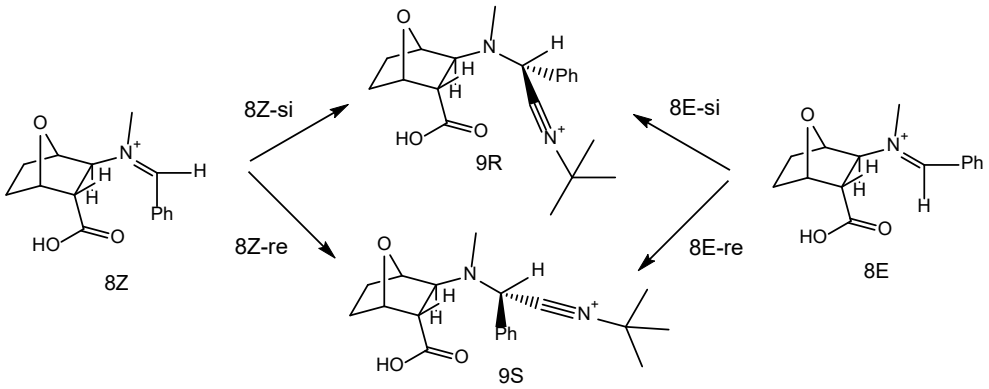
Table 1. Sum of electronic and ZPE (HoF, in Hartree) and relative stabilities (ΔE, in kcal/mol). ΔE of compound was compared to its the most stable relevant isomer.

Compound	Gas Phase		Methanol	
	HoF	ΔE	HoF	ΔE
1	-592.6607897		-592.6741179	
2	-345.3268414		-345.3339299	
3	-250.4343531		-250.4405224	
5R	-938.0076061	0.0	-938.0227511	0.0
5S	-938.0062612	0.8	-938.0207654	1.2
6R	-937.9983689	1.8	-938.0189062	1.4
6S	-938.001178	0.0	-938.0211347	0.0
7R	-937.8430297	4.4	-937.9096266	2.9
7S	-937.8500468	0.0	-937.9142607	0.0
8E	-862.0081159	0.0	-862.0562325	0.0
8Z	-862.002064	3.8	-862.0531642	1.9
9R (8E-si TS)	-1112.425538	0.0	-1112.490257	0.0
9R (8Z-si TS)	-1112.410873	9.2	-1112.479544	6.7
9S (8Z-re TS)	-1112.414137	7.2	-1112.481623	5.4
9S (8E-re TS)	-1112.418801	4.2	-1112.484903	3.4
9R	-1112.447123	0.5	-1112.49916	0.4
9S	-1112.447895	0.0	-1112.499865	0.0
4R	-1188.495176	0.0	-1188.514156	0.0
4S	-1188.4916	2.2	-1188.511984	1.4

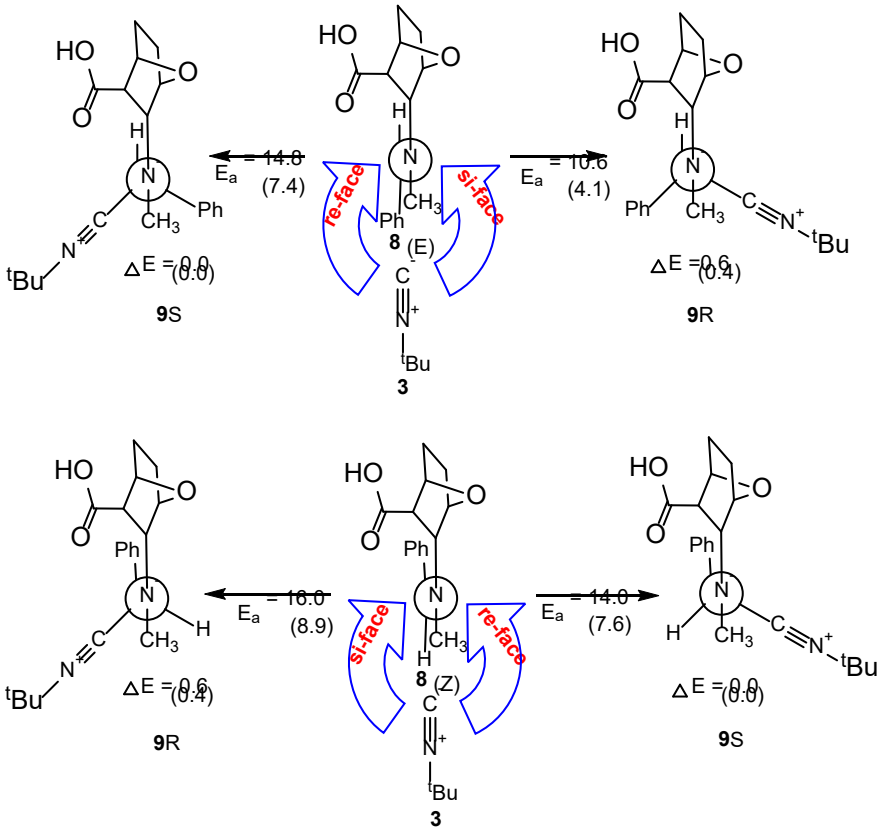
According to the results of calculations, enthalpy of the reaction (ΔH) were -45.9 and -43.7 kcal/mol for **4R** and **4S** respectively which showed that, both products (**4)** of 3C-Ugi reaction were more stable than reagents and the last step was irreversible. In addition, **4R** was 2.2 kcal/mol more stable than **4S**. This result was in agreement with experimental finding that in which **4R** was the predominant isomer (**4R:4S**, >95%) [14].

Considering relative stabilities of intermediates proposed in the mechanism showed that, hemiaminal **5R** was 0.8 kcal/mol more stable than **5S** isomer. Conversion of hemiaminal **5** to iminium ion (**8**) is catalyzed by both Brønsted and Lewis acids [18]. In this case, carboxylic acid group of **1** could provide this proton by intramolecular H-bonding to OH group via conformer **6**. In this situation **6s** was 1.8 kcal/mol more stable than **6R** and provided proper orientation for proton transfer. Intermediate **7** was formed through proton transfer from carboxylic acid to OH group. Between two diastereomers of **7**, **7R** was 4.4 kcal/mol more unstable than **7S**. Both **7R** and **7S** are able to accomplish C-N bond rotation and N-atom inversion before dehydrating to produce **8** in both Z- and E-forms. **8E** was 3.8 kcal/mol more stable than **8Z** isomer and consequently has better chance to exist in equilibrium and approach isocyanide (**3**). Stereoselectivity of 3C-Ugi reaction was originated from an attack of isocyanide to nonequivalent re-face and/or si-face of asymmetrical iminium cation (**8**) (Scheme 3). To explain the diastereoselectivity of this reaction,

structures of isomers of **3**, **8**, **9** and transition states (**8Z**-si TS, **8E**-si TS, **8Z**-re TS and **8Z**-re TS) were optimized (Figure 1 and Table 1). In nomenclature of transition states, for example, **8Z**-si TS means a transition state formed from an attack of isocyanide **3** to the si-face of iminium ion **8Z**. Conformational analysis of **8E** and **8Z** showed that in the most stable conformer, carboxylic acid group was located at re-face of **8E** and si-face of **8Z**. So, si-face of iminium **8E** and re-face of **8Z** were easy path to get to isocyanide **3** (Figures 1 and 2a). Relative energy (ΔE in kcal/mol, **9S** was compared to **9R**) and activation energies (E_a, kcal/mol) of each pathwy were represented in Scheme 4 and corresponding results for calculation in methanol were displayed in parenthesis. Consistent with optimized structures of transition states represented in Figure 1 and supporting information file, isocyanide 3 was located at 2.1-2.2 Å and 106-107° of iminium group of intermediate **8**.



Scheme 3. Potential routes of isocyanide addition to asymmetric iminium ion.



Scheme 4. Isocyanide addition to asymmetric iminium ion. Relative energy (ΔE in kcal/mol, **9**S was compared to **9**R) and activation energy (E_a) are in kcal/mol. Corresponding results for calculation in methanol are represented in parenthesis.

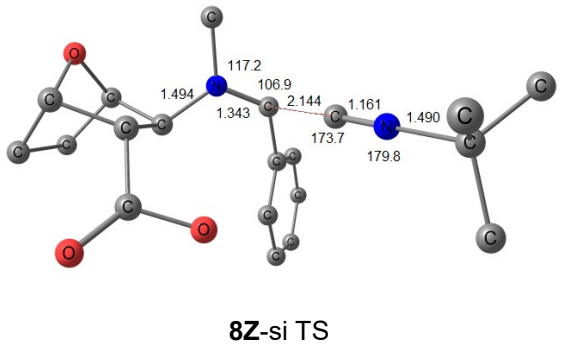
Starting from **8Z**, the calculated activation energy to produce **9S** (E_a = 14.0 kcal/mol) was less than the activation energy of **9R** (E_a = 16.0 kcal/mol). Accordingly, **8Z** prefers to yield **9S** which is not a major product in this reaction. Therefore, proposing **8Z** as key intermediate could not explain the observed diastereoselectivity of the reaction.

Comparing these results with those came from **8E**, as another intermediate, showed that activation energy to produce **9S** (E_a=14.8 kcal/mol) was greater than **9R** (E_a=10.6 kcal/mol). Consequently, the reaction chose **8E** to **9R** pathway having the shorter obstacle. On the other hand, **9R** is slightly (ΔE = 0.5 kcal/mol) less stable than **9S**. Therefore, the stereochemistry of reaction was under kinetic control of addition of isocyanide to iminium ion.

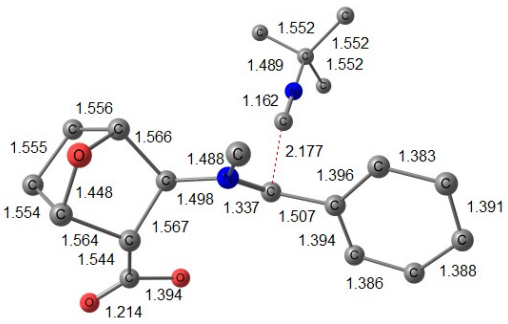
Usually 3C-Ugi reaction is carried out in methanol as a solvent [14]. To study the effect of solvent on the outcome of reaction, single-point calculation carried out at the same level of theory in Polarizable Continuum Model (PCM) solvent utilizing methanol. The trend of results in methanol was in agreement with gas phase. Heats of formation showed that all calculated compounds were more stable in methanol than gas phase. Relative energies of compounds were less in methanol compared to gas phase.

In terms of addition step of isocyanide to iminium ion, **8E** was 1.9 kcal/mol more stable than **8Z**. Among transition states, **8E**-si TS was the most stable and **8Z**-si TS the least transition state (ΔE = 6.7 kcal/mol). Activation energy of formation of **9R** through **8E**-si TS decreased meaningfully to 4.1 kcal/mol in methanol white it was 10.6 kcal/mol in gas phase (Table 1 and Figure 2b). This decline in activation energy enhanced diastereoselectivity of 3C-Ugi.

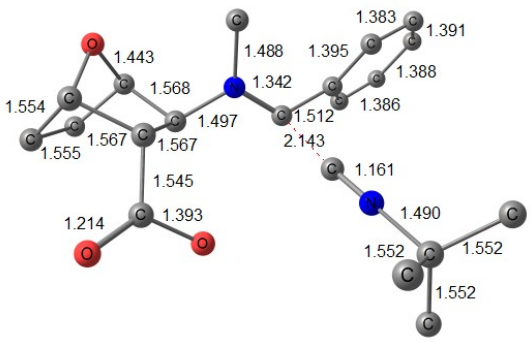
Comparison of calculated results with experimental findings (**9R** as the predominant product (>95%)) showed that in this instance, reaction from si-face of (E)-imine has been the favorite pathway kinetically for diastereoselective 3C-Ugi reaction (Figure 2). To conclude, it seems that different N-substituents on asymmetric amine (**1**) could determine the priority of (E)-imine face to approach isocyanide and accordingly control diastereoselectivity of Ugi reaction.



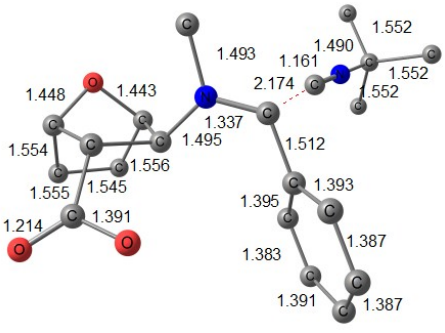
8Z-si TS



8E-si TS



8E re TS



8Z re TS

Figure 1. Optimized structures of transition states involved in 3C-Ugi reaction in gas phase.

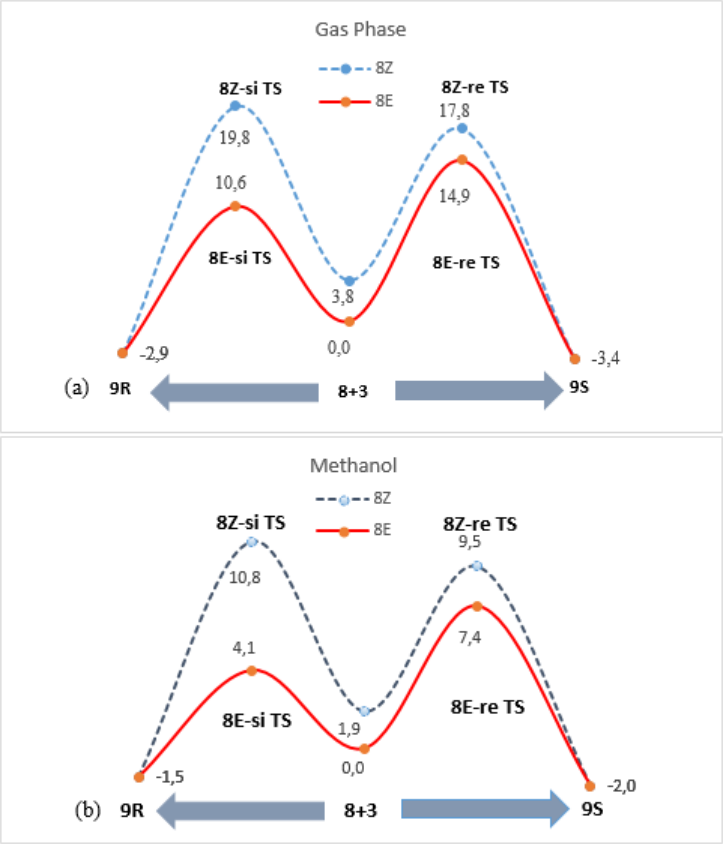


Figure 2. Relative stabilities (ΔE, in kcal/mol) of the intermediates and relevant transition states in (a) Gas phase (b) Methanol.

3. Material and Methods

Structures of compounds involved in 3C-Ugi reaction were fully optimized with the internal 6-31+g(d,p) basis set [19, 20], and DFT (M062X) method [22] procedures implemented in Gamess software [21]. Vibrational frequencies were calculated for all geometries, which were confirmed to have a zero imaginary frequency for reagents and products and one of the transition states. The frequencies were scaled by a factor of 0.9804 for DFT method and used for computation of the zero-point Vibrational energies [23]. Reagents and products were re-localized starting from the transition states by IRC calculations. Sum of electronic and zero point energies (in a.u.) were considered to compare relative stabilities (in kcal/mol). Single-point calculations carried out in PCM solvent utilizing methanol as a common solvent for 3C-Ugi reaction to compare solvent effect with gas phase results. Sum of electronic and zero point energies were presented in supporting file along with Cartesian coordinates of optimized geometry of each structure in gas phase. Relative stabilities were summarized in Table 1. The energy of the most stable isomer was considered as a reference to calculate the relative energy for other relevant isomers.

4. Conclusions

In summary, DFT calculations provided a picture of geometries of components involved in 3C-Ugi reaction especially in terms of stereochemistry. The stereoselectivity of Ugi reaction was under kinetic control. So that, the (E)-geometry of an asymmetrical iminium ion and si-face oriented attack of isocyanide was postulated as the key intermediate to explain the diastereoselectivity of 3C-Ugi reaction in the presence of a chiral amine. This theoretical prediction may provide insights for organic chemists to design novel products for 3C-Ugi reaction considering desired stereochemistry.

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