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ARTICLE

Stereoselective synthesis of functionalized 1,2,3,4-tetrahydroisoquinolines (THIQs) *via* highly diastereoselective Ugi three-component reactions (U3CR) with chiral 3,4-dihydroisoquinolines (DHIQs)

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A highly diastereoselective Ugi three-component reaction (U3CR) involving chiral 3,4-dihydroisoquinolines (DHIQs), isocyanides and carboxylic acids has been developed to synthesize enantiopure 1,2,3,4-tetrahydroisoquinolines (THIQs). The inherent chirality of DHIQ at C-3 and C-4 controles the addition of isocyanide at C-1 to induce excellent diastereoselectivity. The method was applied to a variety of aromatic and aliphatic acids, and in most cases reaction proceeded smoothly without formation of any side product. The experimental and computational studies demonstrated the role of internal chirality in conformational stability of intermediate to control the facial selectivity and strong solvent effect on the reaction. Cytotoxicity of selected compounds was also evaluated against four types of human cancer cell lines MCF-7 (Breast cancer), MDA MB-231 (Breast cancer), DU-145 (Prostate cancer), A549 (Lung cancer) and HepG2 (Liver cancer) where few compounds exhibited GI50 values in submicromolar range.

Introduction

Multicomponent reactions (MCRs) allow rapid construction of small molecule libraries from common starting materials by combining economic and environmental aspects in single step.[1] Ugi reaction is one of the most widely explored MCRs where an isocyanide reacts with *in situ* generated iminium ion to provide interesting peptidomimetic compounds.[2] Various internal imine containing substrates such as dihydroquinoline, dihydroisoquinoline and dihydrobenzoazepines etc have been successfully employed to Ugi three component reactions (U3CR) to obtain functionalized heterocycles.[3,4] Aromatic imines such as quinolines, isoquinolines or pyridines are not reactive towards isocyanide based MCRs, except 1,3-dipolar cycloadditions with aldehydes, malononitrile, and isocyanides.[5] One of the major drawback of Ugi reaction is poor stereoselectivity during isocyanide addition to iminium ion. Although many efforts have been made to develop enantio-/diastereoselective Ugi reactions, excellent selectivity was observed only in a few cases.[6] While good diastereoselectivity remains challenging in open systems, excellent selectivity was observed where chiral cyclic imines were subjected to U3CRs reflecting strong stereo induction from inherent chirality.[7-9] Particularly in the case of chiral pyrrolines, strong stereoinduction was observed in U3CR.[10] In a computational study, Codee *et al* found that the conformation of iminium intermediate is determined by its substitution pattern, controlling the selectivity in isocyanide addition to dictate the chirality at new center.[11] A combination of biocatalytic desymmetrization of chiral cyclic imines with MCR has been developed by several groups for the stereoselective synthesis of substituted pyrrolidines.[12] Furman *et al* synthesized a series of polyhydroxylated piperidines and pyrrolidines by employing sequential lactam reduction/Joullié-Ugi reactions of their lactam counterpart.[13] The use of chiral acids to attain the diastereoselectivity did not show encouraging results.[14] Though U3CR with various chiral cyclic imines have been studied, a diastereoselective U3CR with chiral 3,4-dihydroisoquinoline have not been reported to the best our knowledge.

1,2,3,4-tetrahydroisoquinoline (THIQ) fused piperazines are widely found in many class of alkaloids such as Ecteinascidin **I**,[15] Saframycin; **II**,[16] Naphthyridinomycin; **III**[17] and quinocarcin; **IV**[18] (Figure 1). Though 1,3-*cis* configuration is most common in naturally occurring THIQ containing alkaloids,[19] epimers of naturally occurring counterparts such as 3-*epi*-Jorumycin; **V** and 3-*epi*-Renieramycin G; **VI** have been of significant synthetic interest to explore the role of stereochemistry in their pharmaceutical properties.[20]

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†Electronic Supplementary Information (ESI) available: [^{1}H and ^{13}C NMR and HRMS spectra of all the new compounds, COSY and NOESY spectra of compounds **5a**, **7** and **11**, details of computational studies (Cartesian coordinates and absolute energies).See DOI: 10.1039/x0xx00000x

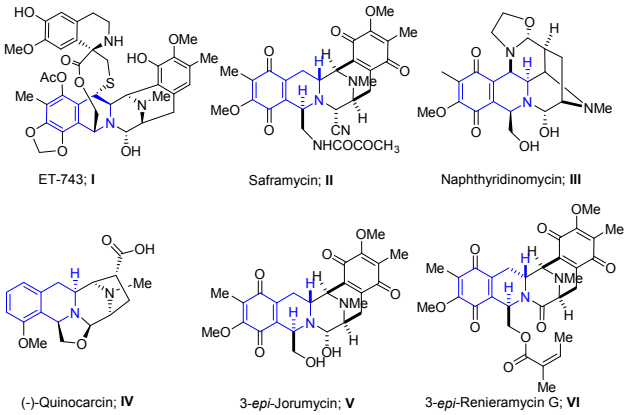
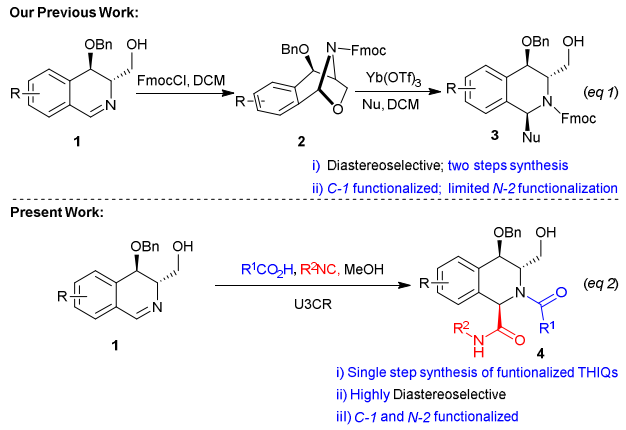


Figure 1. Important alkaloids with chiral THIQ skeleton

Generally the advanced synthetic intermediate of these complex alkaloids consist of a suitably substituted 1,2,3,4-tetrahydroisoquinoline (THIQ) skeleton with requisite chirality.[21] Therefore asymmetric synthesis of functionalized THIQ has attracted synthetic chemists to develop newer methods.[22] Recently, we have developed a novel method to synthesize 1,2,3,4-THIQ **3** from 3,4-dihydroisoquinoline **1** via bridged oxazolidine intermediate **2** by employing Lewis acid catalyzed diastereoselective nucleophilic substitution reactions (eq 1).[23] This method offered an excellent method to obtain *C-1* functionalized THIQs, however substitutions at *N*-2 were limited and required protection-deprotection operations for further applications in total synthesis.[23]

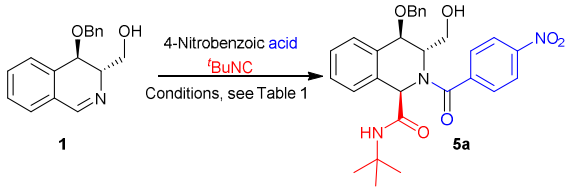


In order to develop efficient synthesis of THIQ containing alkaloids, various functionalizations at N-2 are required with diastereoselective derivatization at C-1. We envisioned that the inherent chirality of C-3 and C-4 may significantly induce chirality at C-1 leading to the desired diastereoselectivity under U3CR conditions (eq 2). Herein, we report a highly diastereoselective Ugi three-component reactions of DHIQ **1** to synthesise a variety of enantiopure THIQs **4** to introduce a wide range of substitutions at N-2. Detailed mechanistic investigations including computational studies were performed and results are summarised. In addition functionalization of one Ugi product and anti-proliferative properties of selected Ugi products have been evaluated.

Results and discussion

DHIQ **1** was easily obtained from Garner's aldehyde in three steps by employing our reported procedure.[23] Trial U3CR involving DHIQ **1**, *tert*-butylisocyanide and *p*-nitrobenzoic acid in methanol did not show any progress at lower temperature (-40 – 0 °C), however a clean formation of product **5a** was observed at room temperature (Table 1, entry 1 – 4). It was interesting to note that the reaction was highly dependent on solvents and in toluene no characterizable product was observed with consumption of all the starting material. Formation of desired product was confirmed by ^{1}H NMR analysis where the *C-1*-H at newly generated stereogenic center was visible at δ 5.28 ppm and *C-1*-H (imine proton) signal of DHIQ **1** disappeared from δ 8.32 ppm. The ^{1}H NMR of purified **5a** showed two signals for *C-1-H* at δ 5.28 (major) and 5.17 (minor) corresponding to the two rotamers that was further confirmed by NOE experiments, while the two signals for *C-1-H* at δ 5.28 (major) and 5.79 (minor) in the ^{1}H NMR of post aqueous work-up sample (crude sample) corresponds to the two diastereomers (*C-1* epimers) [See the supporting information].

Table 1: Reaction optimization



Entry	Solvent	Temp	Time	Yield (%)[a]
1	MeOH	–40 °C	20h	NR
2	MeOH	–20 °C	20h	NR
3	MeOH	0 °C	20h	NR
4	MeOH	rt	15min	89
5	EtOAc	rt	15min	5
6	MeCN	rt	15min	27
7	THF	rt	15min	11
8	DMF	rt	15min	26
9	Toluene	rt	20h	0[b]

[a]Isolated yield of major diastereomer **5a**. Progress of the reaction was monitored by TLC. [b]Starting material (SM) consumed but no characterizable product obtained. NR – No reaction, SM recovered.

Stereochemistry of **5a** at *C-1* position was established by performing 2D-COSY and 2D-NOESY experiments which confirmed it to be 1-*R*, possibly generated through addition of *tert*-butylisocyanide from *Si* face of C-1 (*β*-attack) (Figure 2). ^{1}H NMR spectrum of **5a** displayed two sets of resonances with 16:1 ratio that indicates the presence of minor isomer which was confirmed to be rotamer due to the amide bond present at piperidine ring that could lead to two sets of resonances in

^{1}H NMR spectrum. These resonances showed exchange cross peaks between the minor and major peaks in the NOESY spectrum which confirms that the second set of resonances are appearing because of rotational isomerization.[24]

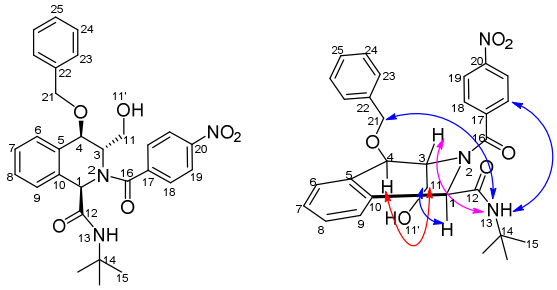


Figure 2. NOE correlations of compound **5a**

The appearance of strong NOE cross peaks between H-1/H-11 and H-1/H-11' along with the small coupling constant between H-3 and H-4 (3J H-3–H-4 = 2.8 Hz) indicate the piperidine ring adopts a half chair conformation having H-1, H-11(H-11') and H-4 protons on one side of the ring as pictorially represented in figure 2.

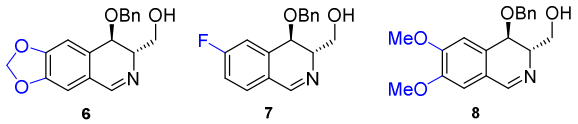
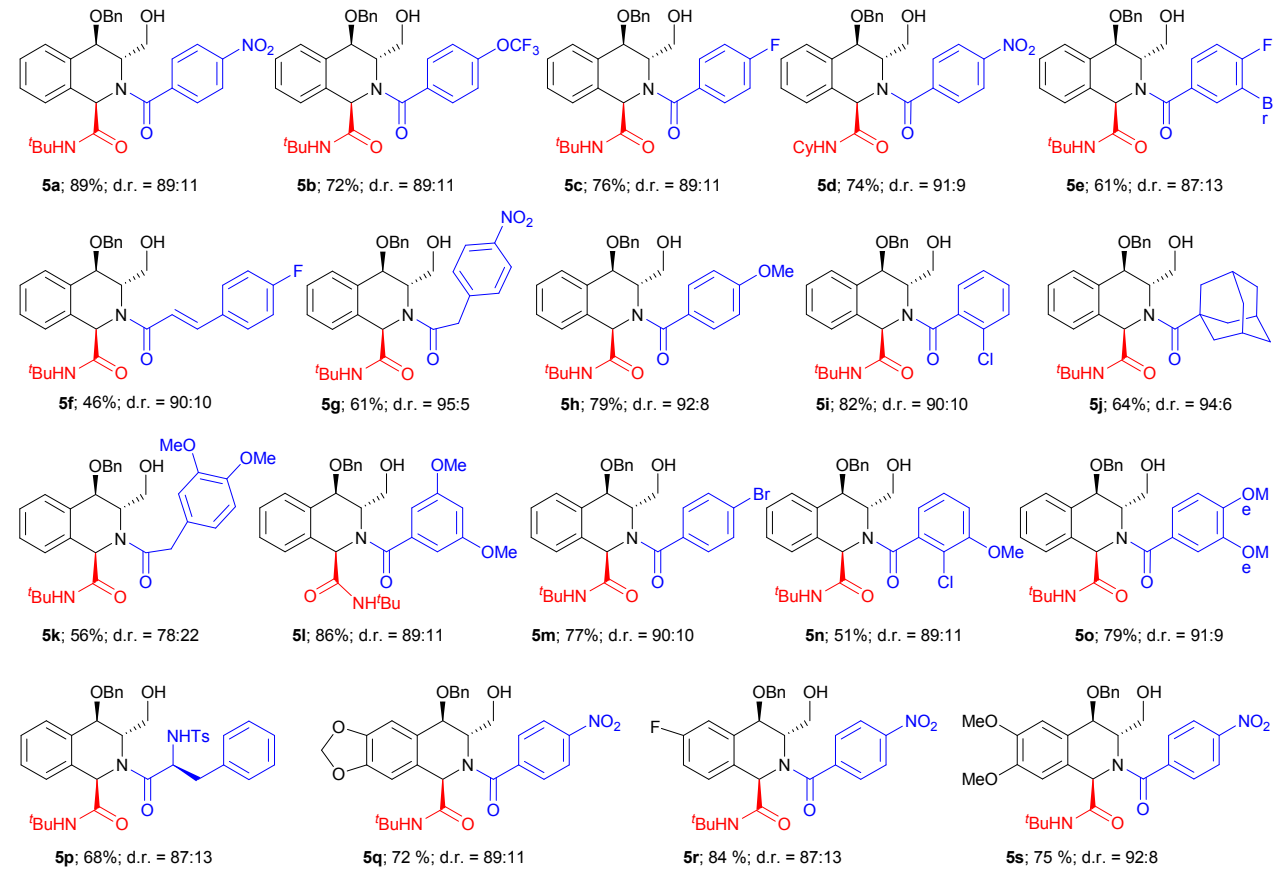


Figure 3. DHIQs used in the study with substitutions at aromatic portion

Further to check the scope of this reaction a series of aromatic, aliphatic and amino acid derivatives were subjected to Ugi reaction with DHIQ **1** (Figure 4). The diastereoisomeric ratios were confirmed by ^{1}H NMR analysis of post aqueous work-up crude samples. All the products were easily purified by column chromatography and were characterized further by ^{1}H and ^{13}C NMR, Mass, IR and HRMS analysis. Relatively poor yields were observed when cinnamic acid and aliphatic acids were used for U3CR (**5f** and **5k**, Figure 3). Reactions with DHIQs **6**, **7** and **8**, bearing electron withdrawing or electron donating groups on aromatic portion of DHIQ, yielded **5q**, **5r** and **5s** respectively in good yields and high diastereoselectivity (Figure 3 and 4).[23]



5a; 89%; d.r. = 89:11 **5b**; 72%; d.r. = 89:11 **5c**; 76%; d.r. = 89:11 **5d**; 74%; d.r. = 91:9 **5e**; 61%; d.r. = 87:13

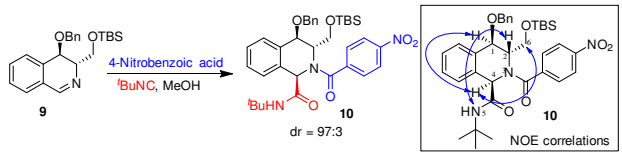
5f; 46%; d.r. = 90:10 **5g**; 61%; d.r. = 95:5 **5h**; 79%; d.r. = 92:8 **5i**; 82%; d.r. = 90:10 **5j**; 64%; d.r. = 94:6

5k; 56%; d.r. = 78:22 **5l**; 86%; d.r. = 89:11 **5m**; 77%; d.r. = 90:10 **5n**; 51%; d.r. = 89:11 **5o**; 79%; d.r. = 91:9

5p; 68%; d.r. = 87:13 **5q**; 72 %; d.r. = 89:11 **5r**; 84 %; d.r. = 87:13 **5s**; 75 %; d.r. = 92:8

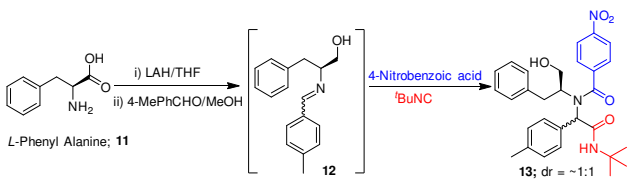
Figure 4. Substrate scope of the reaction [Diastereomeric ratios were determined the ^{1}H NMR analysis of post aqueous work-up crude reaction mixtures. The *C-1*-H at newly generated stereogenic carbon was used to calculate the ratio as it was clearly visible in the region of δ 5.00 – 6.00 ppm without any overlap of peaks from excess reactants. (See supporting information)]

According to our hypothesis, it was important to understand the role of *C-3*-CH_2OH which might be inducing the diastereoselectivity by providing anchimeric assistance. To examine the role of *C-3*-CH_2OH on the stereochemical outcome, U3CR with substrate **9** where OH was protected as silyl ether, was carried out with similar reagents and conditions (Scheme 1). Protection of the alcohol functionality was difficult with other protecting groups such as benzyl, benzoyl etc as DHIQ **1** gets converted to bridged oxazolidines.[23] Ugi reaction of substrate **9** yielded **10** with equally good diastereoselectivity as unprotected DHIQ **1** confirming that *C-3*-CH_2OH did not participate in the reaction through anchimeric assistance by forming bridged oxazolidine.[23]



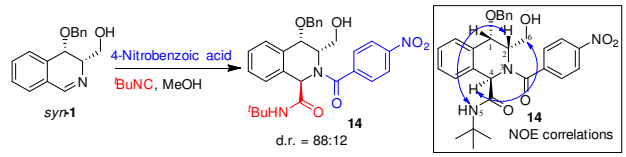
Scheme 1: U3CR with C3-hydroxymethyl protected DHIQ **9**

Another effort to extend this reaction to acyclic substrates with a chiral appendage at *C-2* position did not give encouraging results (Scheme 2). Ugi reaction with acyclic imine **12** which was obtained by LAH reduction of *L*-phenylalanine **11** followed by condensation with *p*-touladehyde gave equal mixture of diastereomers **13,** limiting the scope of present methodology to cyclic substrates (Scheme 2, data not shown).



Scheme 2: U3CR with acyclic imine **12**

Effect of C-4 chirality was also investigated by performing the reaction with *syn*-DHIQ; *syn*-**1**. The reaction gave good diastereoselectivity towards *β*-product **14** (Scheme 3). 1,3-trans configuration was confirmed by 2D-NOESY correlations of **14**.



Scheme 3: U3CR with *syn*-DHIQ (*syn*-**1**)

Computational Studies: To understand the diastereoselective preference of *β* (1*R*) isomer over *α* (1*S*) isomer quantum chemical calculations were performed and the reaction profiles were generated by employing gas as well as solvent (methanol) phases using PCM model at B3LYP/6-31+G(d) level of theory for both *α* and *β* attacks. All the calculations were performed using Gaussian 09 program package.[25]

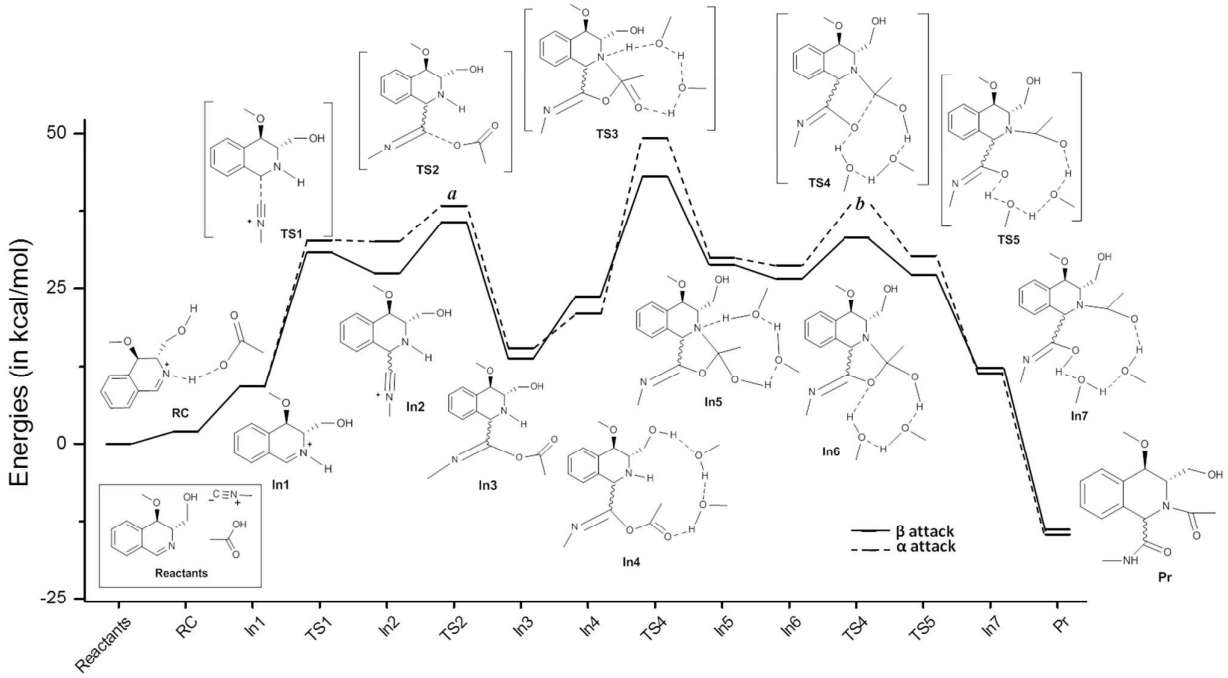


Figure 5: Reaction energy profiles generated at B3LYP/6-31+G(d) level of theory.(obtained by single point calculations using– a: gas phase optimized geometries, b: could not be obtained)

Previous reports show that π-facial selectivity involves various factors such as steric, electrostatic and electronic which work in concordance and discordance in determining the final product.[26] The bulky groups were substituted with methyl groups to reduce the computational cost. A huge effect of solvent was observed on the reaction path (Figure S1, See Supporting Information). Hence the discussion is carried out analysing the solvent phase results (Figure 5). The mechanism of UGI reaction has been well established previously, therefore we aim to look at the preferential formation of one isomer over the other. The initial trials for generating N–C bond forming TS, O–C bond breaking TS and H-migration TSs were futile. Hence we considered two explicit solvent molecules to generate these TSs. This method was previously employed by Fleurat-Lessard and co-workers.[27] **In3** complexes with the two methanol molecules and forms **In4**. All the trials for generating the C–N bond forming TS and the corresponding intermediate from **In4** were futile which either lead to **In4** or **In5**. Therefore bond critical points (AIM2000 software)[28] were generated for **In4** to understand the nature of bonding (Figure 6). The AIM calculations on the **In4** suggest a bond critical point (BCP) between C•••N, with ρ and its Laplacian values being 0.050 and 0.023 respectively, thereby suggesting that strong interactions exist between C•••N and in turn yield a barrierless TS. This is true for *β* attack while for *α* attack the **In4** does not show a BCP between C•••N. Thus **In4** should generate **In5** via a barrierless N–C bond formation TS and **TS3** which is a proton migration TS.

After generating the reaction profiles for *α* and *β* attacks, we aimed to comprehend the reason for the experimentally formed *β* isomer as major product. Throughout the reaction profile the structures generated for *β* attack are stable compared to *α* attack by ~1 to 6 kcal/mol except for **In4** and **In8**. Assuming that the initial attack of the isocyanide must be a deciding factor for the reaction to proceed forward and in turn generate the final product we focussed on the **RC** and **TS1** structures. **TS1** for *β* attack is ~2.0 kcal/mol more preferred than *α* attack, this however does not give a valid reason for the preferential formation of *β* product. Hence the HOMO and LUMO orbital diagrams of the **RC** were looked (Figure 6). In both HOMO and LUMO the electron density on the orbitals is more concentrated towards the *β* phase suggesting that the isocyanide must attack from the *β* side. Further bond critical points were generated for **TS1** considering both *α* and *β* attacks (Figure 5). **TS1** generated by *β* attack shows BCP between CH_3O•••$CNCH_3$, with ρ and its Laplacian values being 0.008 and 0.007 respectively, suggesting weak interactions which stabilize the TS while the **TS1** for *α* attack is devoid of these interactions. Also the ρ and its Laplacian values, and the bond lengths suggest that the **TS1** considering *α* attack is a tight TS while for *β* attack is loose TS which in turn suggests the preferred attack of *β* over *α*.

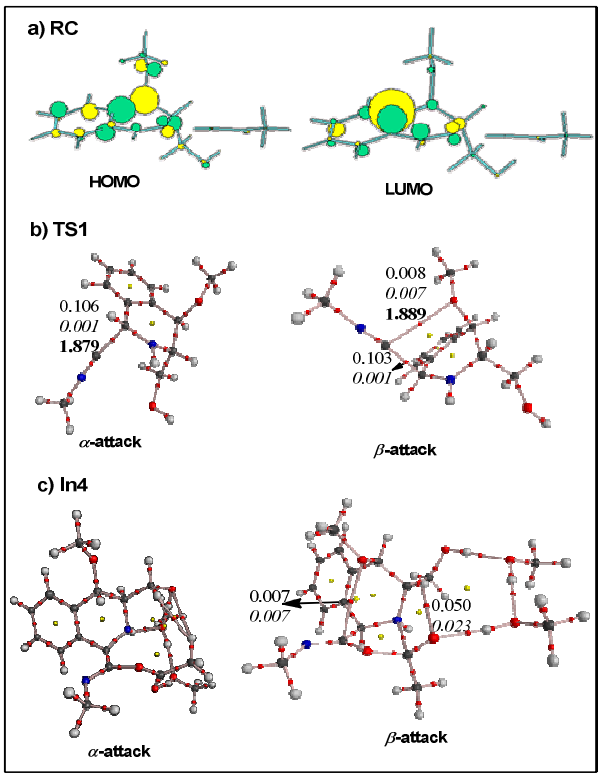


Figure 6: HOMO and LUMO orbital diagrams for **RC** along with bond critical points generated for **TS1** and **In4** considering *α* and *β* attacks. (normal :ρ, italics : Laplacian of ρ, bold : bond lengths in Å.)

Plausible Mechanism: Considering the findings from computational studies and related experiments, a plausible mechanism has been elucidated in figure 7. The activation of imine followed by favourable attack of isocyanide from *Si* face to yield the transient reactive intermediate **A** which reacts with acid to form more stable reactive intermediate **C** which then rearranges to the desired product. Formation of bridged oxazolidine intermediate[23] was ruled out on the basis of observations from experiments shown in scheme 1.

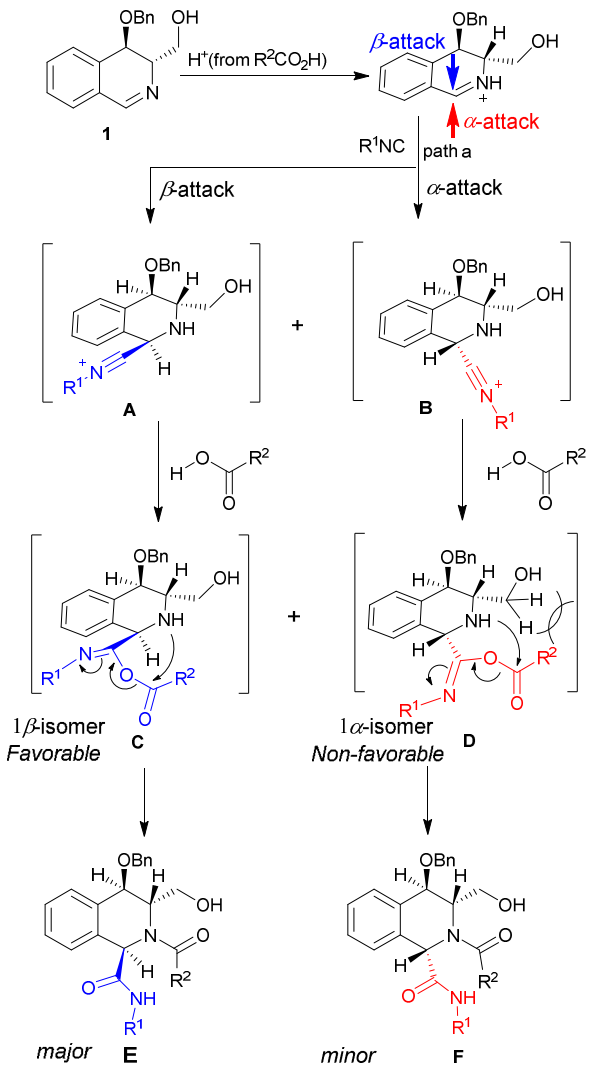
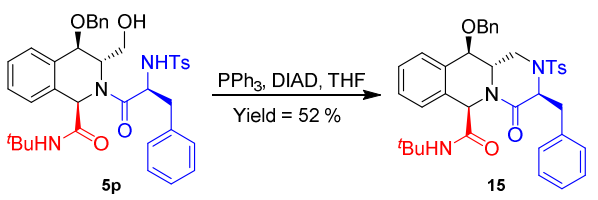


Figure 7: Plausible mechanism

In order to explore the application of present methodology, intramolecular Mitsunobu reaction was performed with compound **5p** to obtain THIQ fused piperazinone **15** in good yield (Scheme 4). THIQ fused piperazinones are highly abundant in natural products and have been widely used in total synthesis.[29]



Scheme 4: Preparation of hexahydropyrazinoisoquinolinone

Anticancer activity: To reflect the pharmaceutical significance of synthesized THIQs, cytotoxicity profile of selected compounds were evaluated against four types of human cancer cell lines such as MCF-7 (breast cancer), MDA-MB-231 (breast Cancer), DU-145 (prostate cancer), A549 (lung cancer) and HepG2 (liver cancer) [Table 2].[30] Compounds **5a**, **5d**, **5g**, **5i** and **5p** exhibited good anticancer profile against most of the cancer cell lines. The GI_{50} values were encouraging and infer that suitable modification of substituent may lead to some potential anticancer hits.

Table 2: Cytotoxicity data of selected compounds

Entry	Compound	GI_{50} (μM)				
		MCF-7	MDA MB-231	DU-145	A549	HepG2
1	**5a**	4.148	6.883	5.813	12.48	7.690
2	**5b**	9.419	11.34	20.16	18.00	13.42
3	**5c**	8.941	12.81	18.29	21.09	12.90
4	**5d**	2.467	2.629	4.500	7.358	5.417
5	**5e**	4.031	9.167	12.21	28.16	11.91
6	**5f**	4.644	7.755	7.971	25.41	11.26
7	**5g**	2.000	2.558	2.273	4.964	4.898
8	**5i**	3.257	4.902	7.370	27.31	8.038
9	**5p**	2.364	3.615	5.939	9.677	6.320
10	**11**	5.500	1.622	10.42	54.33	9.114
11	Doxorubicin	1.026	2.122	0.955	1.951	1.487
12	Tamoxifen	8.083	11.73	19.33	24.42	21.78

MCF-7 (Breast cancer), MDA MB-231 (Breast cancer), DU-145 (Prostate cancer), A549 (Lung cancer) and HepG2 (Liver cancer)

Conclusions

A concise and highly stereoselective synthetic route for the construction of densely functionalized enantiopure 1,2,3,4-tetrahydroisoquinolines (THIQs) from 3,4-dihydroisoquinoline has been explored by employing Ugi three-component reactions. This methodology is efficient and robust enough to produce a diverse collection of biologically relevant 1,2,3,4-tetrasubstituted THIQs. Detailed experimental as well as computational studies were performed to understand the required elements causing high diastereoselectivity. Considering the challenges in attaining excellent diastereoselectivity in one of the most widely used Ugi reactions, we believe that the outcomes of present methodology will render solutions to synthesize complex alkaloids. We utilized the inherent chirality of Garner's aldehyde through 1,2- and 1,3-/1,4-asymmetric inductions to obtain fully functionalized THIQs without any external chiral sources. This novel method can be useful for the synthesis of THIQ-containing chiral bioactive natural products and their derivatives. Cytotoxicity data of selected compounds reflected the pharmaceutical potential of these THIQs.

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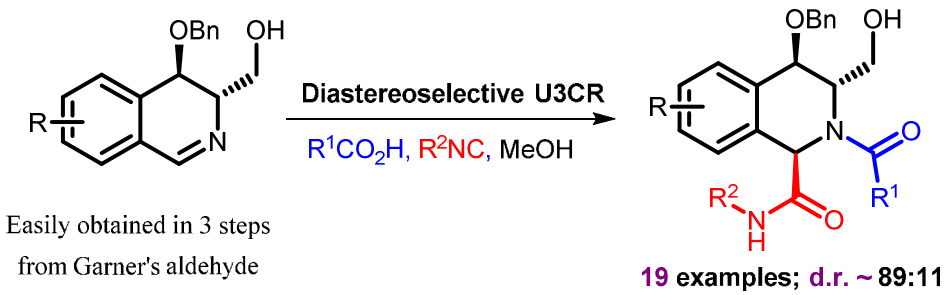
Table of Contents Graphic



Easily obtained in 3 steps from Garner's aldehyde

19 examples; d.r. ~ 89:11

Highly diastereoselective Ugi three-component reaction (U3CR) of chiral 3,4-dihydroisoquinolines has been developed to synthesize enantiopure 1,2,3,4-tetrahydroisoquinolines (THIQs).