First synthesis of fused-Δ^1-pyrrolines *via* intramolecular 1,3-dipolar cycloaddition of ketoimine: A complete diastereoselective approach†

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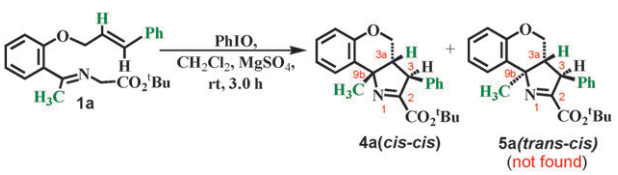
Intramolecular formal 1,3-dipolar cycloaddition of ketoimine is developed with PhIO for the first synthesis of fused-Δ^1-pyrrolines. The scope of the reaction, complete diastereoselectivity and its rationalization by a computational study are reported.

1,3-Dipolar cycloaddition (DC) is an extremely powerful atom-economical strategy in organic chemistry and its allied branches of science toward construction of novel heterocyclic scaffolds.[1–4] Relative to the conventional method, Lewis acid controlled 1,3-DC offers a significant improvement in the reaction rate, the regioselectivity and/or stereoselectivity. In this regard, an intramolecular approach is more interesting due to the favorable entropy and conformational restriction in its transition state. 1,3-DC of an azomethine ylide derived from aldimine has been intensely studied to afford a pyrrolidine moiety.[2] Surprisingly the use of ketoimine has received only scant attention.[3] Generation of azomethine ylides from ketoimines and their intramolecular 1,3-DC with an olefin with a tandem elimination process under an organic Lewis acid *cum* oxidant has never been realized. This approach would be attractive since it can achieve the first synthesis of fused-Δ^1-pyrroline. In a continuous effort to synthesize novel heterocyclic functional molecules[1c,5] especially under metal-free mild reaction conditions, we have developed novel properties of iodosobenzene (PhIO) to synthesize isoxazolines,[5a] imidazoles[5b] and 1,2,4-triazoles.[1c] Expanding the interest of this powerful reagent in a most fascinating synthetic approach, we herein report the straightforward access of fused-Δ^1-pyrroline (**4**) by the intramolecular formal 1,3-DC of ketoimine (**1**, Scheme 1) with PhIO. The excellent Lewis acid property of PhIO has displayed exceptional stereoselectivity in the cycloaddition step and broad scope toward other rapidly accessible and valuable heterocycles.

Δ^1-Pyrrolines and their analogues have found broad applications as pharmaceuticals, pesticides, agrochemicals and devices.[6,7] They have widespread availability in roasted flavor foods, natural products and biosynthetic intermediates.[7] The presence of a prochiral imine functionality and three stereogenic centers in its skeleton have made it a versatile synthon toward varied biologically active compounds.[8,9] Synthesis of Δ^1-pyrrolines is mainly addressed by metal Lewis acid catalyzed intermolecular 1,3-DC of nitrile ylides, azaallyl anions, azalactones,[10] cyclization[9] and photochemical reactions.[11]



Scheme 1 Construction of fused-pyrroline by 1,3-DC of ketoimine.

Table 1 Development and optimization of the reaction[a]

Entry	Reagent[b]	Reaction conditions	Conversion(%)	**4**, Yield(%)
1	$PhI(OAc)_2$	CH_2Cl_2, rt, 10 h	No reaction	—
2	$PhICl_2$	CH_2Cl_2, rt, 10 h	No reaction	—
3	PhIO-TMSOTf	CH_2Cl_2, −80 °C, 2.5 h	Decomposed	—
4	PhIO	CH_2Cl_2, rt, 3 h	100	67[c]
5	PhIO	THF, rt, 3 h	100	66[c]
6	PhIO	MeCN, rt, 3 h	100	67[c]

[a] Isolated yield (**4a**). [b] 1.25 mol. [c] Hydrolysed to ketone (~10–15%).

We have started our study with the ketoimine **1a** as the model reaction for screening several hypervalent iodine(III)[12] reagents as organic Lewis acids. Most commonly used $PhI(OAc)_2$, $PhICl_2$ and PhIO-TMSOTf[13] are not effective (entries 1–3, Table 1). Gratifyingly, under the neutral and mild reaction conditions PhIO served as an optimum Lewis acid for a cascade cyclization process to furnish the desired fused-pyrroline (**4a**). Poor solubility of PhIO in common organic solvents is explained due to its bridged polymeric structure involving an intermolecular I···O interaction.[12] However, it dissolves smoothly with progress of the reaction (entries 4–6).

With this initial success, the substrate scope of the formal cycloaddition reaction was explored with a small series of precursors (**1b–g**, entries 1–6, Table 2) toward rapidly (2.0–5.0 h) accessible fused-Δ^1-pyrrolines (**4b–g**) with moderate yields (60–80%). We were surprised to see that only the ethyl ester group in **4c** (entry 2) was hydrolyzed, whereas other ester groups were tolerated. Only one cycloadduct was found in each individual case (entries 3–6) possessing ***cis*** absolute selectivity at the newly generated C-C bond bearing a quaternary stereogenic center, C_{9b}. Surprisingly, the 1,3-DC reaction of *O*-cinnamyl precursors (**1a–c**) produced only one diastereomer (**4a–c**) with ***cis–cis*** (C_{3a}-*H*-C_{9b}-CH_3 and C_3-*Ph*-C_{3a}-*H*) stereogenic centers. The structure was determined by means of single crystal X-ray diffraction studies (**4a**, Fig. 1)[14] and spectroscopic analyses (see ESI†). The moderate yield might be attributed to the hydrolysis of ketoimines[15] (10–15%) by the water molecule generated during the oxidative dehydration process. Fabrication of nanostructured organic materials involving noncovalent weak interactions of the fused-heterocyclic scaffolds is in progress (see ESI†).[5b,c]

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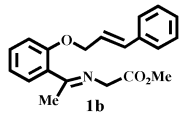
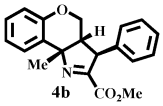
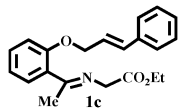
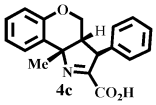
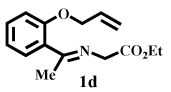
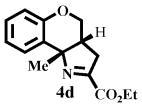
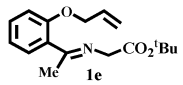
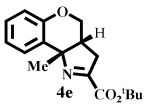
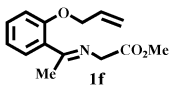
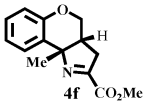
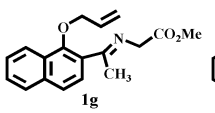
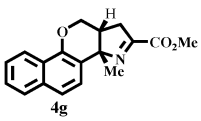
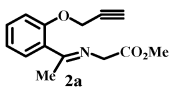
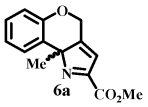
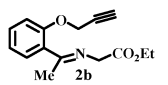
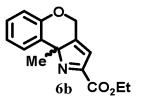
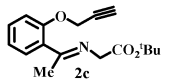
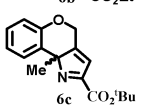
† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra, characterization, DFT data, CIF file and studies of weak noncovalent interactions. CCDC 773893. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03873c

Table 2 Synthesis of fused-pyrroline (**4**) and pyrrole (**6**)

Entry	Ketoimine	Pyrroline, Pyrrole	Time(h)	Yield(%)
1	 **1b**	 **4b**	3	70
2	 **1c**	 **4c**	2	80
3	 **1d**	 **4d**	5	62
4	 **1e**	 **4e**	4	71
5	 **1f**	 **4f**	3	60
6	 **1g**	 **4g**	5	61
7	 **2a**	 **6a**	4	70
8	 **2b**	 **6b**	5	72
9	 **2c**	 **6c**	4	62

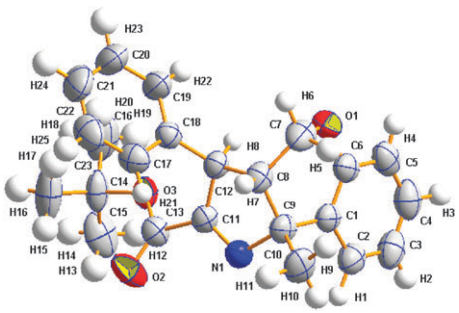
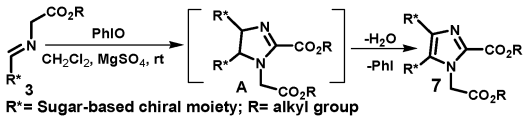
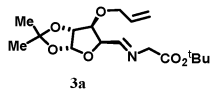
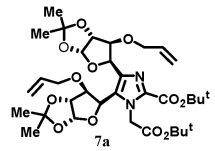
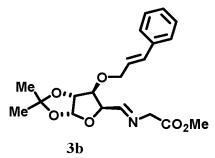
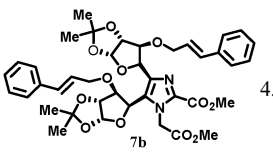
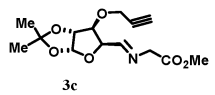
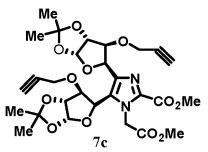
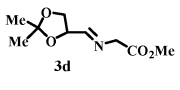
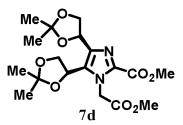
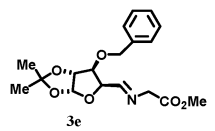
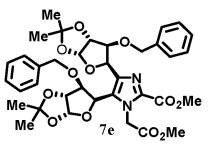


Fig. 1 Single crystal X-ray diffraction structure of **4a**.

To evaluate the scope and generality of the metal-free simple synthetic protocol, the intramolecular 1,3-DC reaction of unactivated propargylic precursors (**2a–c**, entries 7–9) was investigated. This afforded very uncommon heterocyclic scaffolds of fused-2*H*-pyrroles (**6a–c**) possessing quaternary centers (C_{9b}) with fast reaction rates (4–5 h) and moderate yields (62–72%). Fused and highly substituted pyrroles are important structural elements of many natural products and have found widespread applications in medicinal chemistry, catalysis and material science.[16]

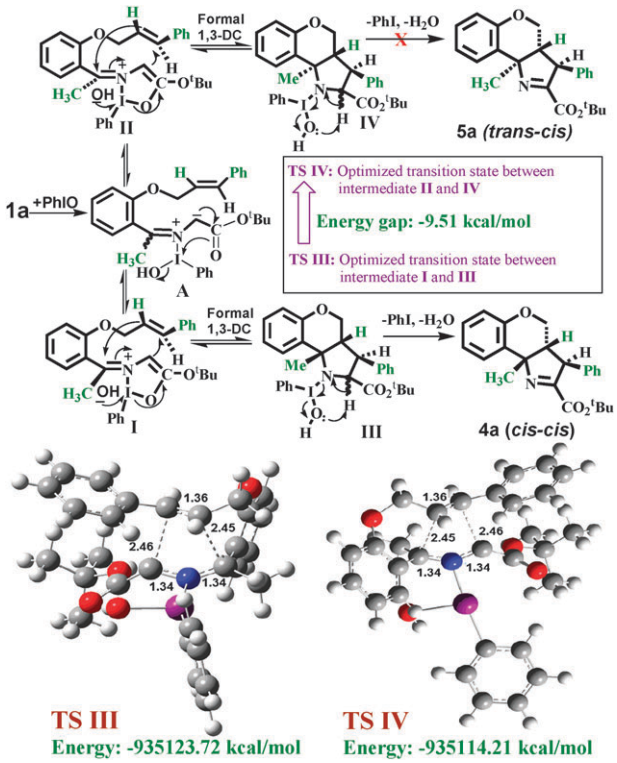
Table 3 Construction of chiral imidazole from aldimine



Entry	Chiral imine	Sugar-based chiral imidazole	Time (h)	Yield (%)
1	 **3a**	 **7a**	5.0	82
2	 **3b**	 **7b**	4.0	82
3	 **3c**	 **7c**	5.0	80
4	 **3d**	 **7d**	4.0	72
5	 **3e**	 **7e**	3.5	78

However, an azomethine ylide-hypervalentiodane complex of aldimine did not react with the olefin[5b] to follow the intramolecular 1,3-DC pathway of ketoimine. It rapidly (3.5–5.0 h) underwent intermolecular formal cycloaddition with a strongly electron donating imine. Such an extraordinary Lewis acid *cum* oxidation property of PhIO was utilized to achieve highly functionalized sugar-based chiral imidazoles (**7**, Table 3) in excellent yields (72–82%). Installation of two sugar units was achieved side-by-side. The structure was determined by means of single crystal X-ray diffraction analysis (see ESI†). Imidazole is a common heterocyclic scaffold of many natural products and its chiral analogues had found special applications as effective reagents, catalysts, receptors and pharmaceuticals.[17]

In contrast to Grigg's commonly used method for generation of azomethine ylides by 1,2-prototropic shift of α-aldiminoester under strong heating conditions,[4] formation of an azomethine ylide dipolar complex with the powerful organic Lewis acid proceeds through predominant coordination even with the ketoimine (**1a**) at ambient temperature. The PhIO-activated species (**A**) may exist in two alternative highly chelated zwitterionic stereoisomers (**I**, **II**, Scheme 2) with varied orientation of the methyl group. **I** and **II** follow the unidirectional formal [3 + 2]-intramolecular cycloaddition pathway with the olefin involving five membered transition states. The intermediates **III** and **IV** undergo rapid construction of the double bond



Scheme 2 Possible reaction path and DFT study.

Table 4 Geometry optimization of diastereomer **4a** and **5a**

	ab initio	Density functional theory		
Energy	HF/6-31G	B3LYP/ 6-31G	B3LYP/ 6-311G	B3LYP/ 6-311G**
$^{a}\Delta E_{4a-5a}$	−7.85	−6.81	−8.62	−9.01
$^{a}E_{5a}$	−730475.66	−735192.83	−735359.41	−735578.28
$^{a}E_{4a}$	−730483.51	−735199.64	−735368.03	−735587.29

^{a} Energy reported in kcal mol^{-1}.

involving reductive elimination of the hypervalent-iodane moiety toward diastereomers **4a**(***cis–cis***) and **5a**(***trans–cis***). However, **5a** was not found from the post-reaction mixture.

We have carried out geometry optimization of the **4a**(***cis–cis***) and **5a**(***trans–cis***) by both *ab initio* and density functional theory (DFT) as implemented in the Gaussian 03 program.[5a,c,18] Results in Table 4 reveal that **4a** is the thermodynamically stable product. The ground state energy difference (ΔE_{4a-5a}) between **4a** (E_{4a}) and **5a** (E_{5a}) is as high as −9.01 kcal mol^{-1}. However, conformational and steric outcome under kinetic control can be rationalized by comparing the relative geometry and energy optimized transition state **TS III** (between **I** and **III**) with the **TS IV** (between **II** and **IV**) at the formal 1,3-DC step.[5a,18c] Each of the azomethine ylide complexes of 67 atoms including iodine is computed in B3LYP/6-311G** and LANL2DZ[18b] basis sets. **TS III** is found as relatively more stable by −9.51 kcal mol^{-1} compared to **TS IV**. Thus, a lower activation energy barrier for **TS III** drives the formal cycloaddition reaction in favor of the complete diastereoselective synthesis of **4a**.

In conclusion, we have for the first time demonstrated the synthesis of fused-Δ^1-pyrrolines by an intramolecular formal 1,3-DC of ketoimine under an organic Lewis acid *cum* oxidant. The remarkable diastereoselectivity that was found experimentally is predicted by a DFT study. This simple synthetic route is extended toward synthesis of fused-pyrroles and sugar-based chiral imidazoles.

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Notes and references

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