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Visible-Light-Mediated β-C(sp^3)−H Amination of Glycosylimidates: En Route to Oxazoline-Fused/Spiro Nonclassical Bicyclic Sugars

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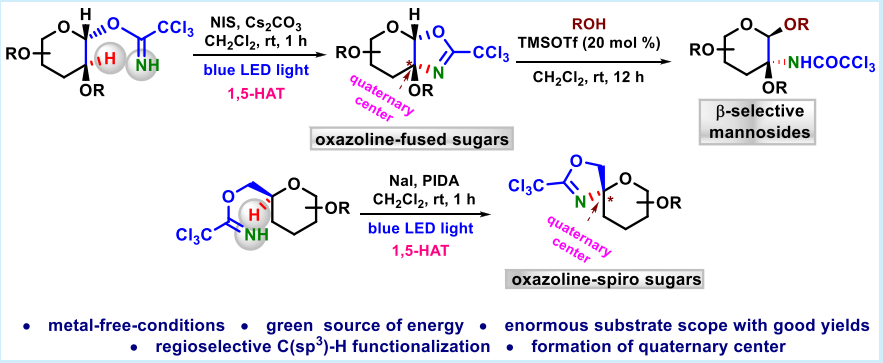
Supporting Information



ABSTRACT: A straightforward route has been developed for the diastereoselective synthesis of nonclassical conformationally constrained oxazoline-fused and spiro bicyclic sugars bearing a quaternary center via selective β-C−H amination of appropriately positioned glycosylimidates. The desired transformation proceeds via the generation of imidate N-radicals under visible-light conditions followed regioselective intramolecular N−C bond formation. The reactions tolerate broad functional groups under the optimized conditions. Furthermore, the synthetic utility of oxazoline-fused bicyclic sugar moiety is demonstrated through the glycosylation reactions.

The incorporation of functionalized heterocycles into the carbohydrate skeleton with the aim to increase the overall chemical and physical properties, such as solubility, reactivity, pharmacodynamics, and pharmacokinetics, is arguably the most fascinating and challenging aspects for organic community.[1,2] Hence, the development of an efficient and robust strategy for the installation of heterocycles to the sugar templates in a one-pot manner using an appropriately functionalized substrate with a viable and straightforward synthetic route is a highly desirable and continuous goal in modern organic synthesis, in particular to carbohydrate chemists. Bicyclic sugars, for instance, oxazoline-fused sugar derivatives, are the key structural units found in many bioactive natural compounds and exhibit glycosidase inhibition activity, antifungal activity, etc.[3,4] However, such modification of the sugar templates, in general, requires multistep and harsh conditions.[5]

Free-radical-initiated reactions provide a practical and straightforward synthetic route for making the desired C−C,[6] C−N,[7] C−O,[7] and C−X (X = Cl, Br, I)[8] bonds, which are in accordance with the parameters of sustainable chemistry such as high atom economy and step economy. In particular, chemoselective and regioselective C−N bond formation via in-situ-generated N-centered radicals (NCRs) from the nitrogen-containing compounds under mild conditions is a high research priority for the chemical community.[9] N-centered radicals serve as key synthetic intermediates for the synthesis of functionalized saturated and unsaturated heterocycles.[10] Generally, NCRs were synthesized from the amide and oxime derivatives after going through the homolytic cleavage of a N−X bond (X = I, Cl, O, S) under hazardous conditions (ultraviolet (UV) light as a source of energy), which eventually hampered the broad application of these methods. Recently, several research groups have successfully generated NCRs from the respective substrate under visible-light conditions and effectively functionalized the unreactive and distal C(sp^3)−H bonds to make new N−C bonds.[11] Recently, Nagib and co-workers[12] and He et al.[13] have elegantly demonstrated the synthetic applications of the NCRs approach to obtain the high-value synthons, where imidate N-radicals were generated from alkylimidate derivatives under suitable conditions (Scheme 1a).

Very recently, we have disclosed a new synthetic method for the construction of diversely functionalized dihydropyrroles from alkylimidate derivatives via activation of benzylic C(sp^3)−H bonds through the imidate N-radicals under visible-light conditions (Scheme 1b).[14] The functionalization of aliphatic methylene C−H bonds, particularly carbohydrates C−H[15] is a much more challenging task in comparison to the benzylic C−H bonds (BDE: aliphatic (98 kcal/mol) vs

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Scheme 1. Different Synthetic Approaches for the Synthesis of High-Value Synthons via Imidate N-Radicals

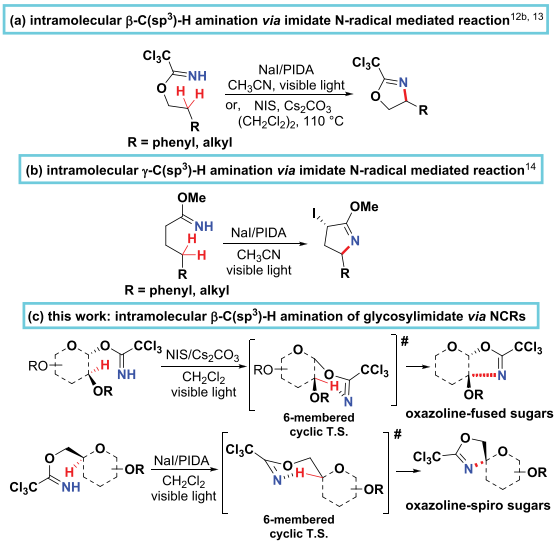
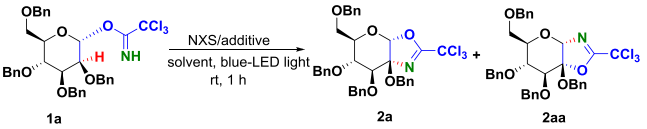


Table 1. Optimization of the Reaction Conditions[a]



			Yield[b] (%)	
entry	reagent (equiv)	solvent	2a	2aa
1	NIS (3)	$(CHCl_2)_2$	n.d.[c]	–
2	NIS (3)/Cs_2CO_3 (3)	$(CHCl_2)_2$	42	18
3	NIS (3)/Cs_2CO_3 (3)	CH_3CN	18	trace
4	**NIS (3)/Cs_2CO_3(3)**	**CH_2Cl_2**	**56 (A)**	**23**
5	NIS (3)/Cs_2CO_3 (3)[d]	CH_2Cl_2	42	29
6	NIS (3)/Cs_2CO_3 (3)	CH_2Cl_2[e]	43	33
7	NIS (3)/K_2CO_3 (3)	CH_2Cl_2	35	6
8	NIS (3)/Ag_2O (3)	CH_2Cl_2	n.d.[c]	–
9	NBS (3)/Cs_2CO_3 (3)	CH_2Cl_2	n.d.[c]	–
10	NCS (3)/Cs_2CO_3 (3)	CH_2Cl_2	n.d.[c]	–
11	NIS (1.5)/Cs_2CO_3 (1.5)	CH_2Cl_2	36	–
12	NaI (3)/PIDA(3)	$(CHCl_2)_2$	33	–
13	**NaI (3)/PIDA(3)**	**CH_2Cl_2**	**52 (B)**	–
14	NaI (1.5)/PIDA(1.5)	CH_2Cl_2	44	–

[a]All the reactions were performed with mannosyl trichloroacetimidate **1a** on a 0.15 mmol at a concentration of 0.1 M at room temperature (rt), using 12 W (× 2) blue LED light for 1 h. [b]Isolated yield. [c]Not determined after 24 h. [d]12 W blue LED was used. [e]Concentration of a solution was 0.05 M.

benzylic (85 kcal/mol)). Because of inherent complexity (electronic and steric) and diverse C−H bonds present in carbohydrate molecules, good control of regioselectivity and stereoselectivity remains an unsolved problem. Therefore, very few reports are available in the literature where carbohydrates C−H bonds were directly functionalized to the desired derivatives.[16]

Considering these facts and our continuing interest[17] in the development of new synthetic methodology for the construction of functionalized organic molecules, we anticipated that the biologically relevant oxazoline-fused and spiro moiety can be rapidly introduced to the different positions of sugar templates in a one-pot manner from appropriately positioned glycosylimidates and eventually offer an appealing way to access conformationally constrained bicyclic sugar derivatives bearing a quaternary center at different positions. Here, we report the regioselective and diastereoselective approach for the synthesis of bicyclic sugars (fused/spiro) via NCRs-mediated remote activation of inert β-C(sp^3)−H bonds of complexed sugar system through 1,5-hydrogen-atom transfer (HAT) (Scheme 1c).

At the outset, we selected 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl trichloroacetimidate **1a** as a model substrate, where the imidate group is appropriately present at the α-position to the aliphatic methylene C2−H bond (α-side) and blue LED light (λ_{max} = 455 nm) as a source of energy and NIS as a halogenating reagent. With this setup of conditions, when the reaction was performed in $(CHCl_2)_2$ solvent for 24 h, unfortunately, no desired product was formed, and several spots were observed on the TLC plate (Table 1, entry 1). Interestingly, the introduction of Cs_2CO_3 in the reaction medium worked well and afforded the desired C1−O-linked oxazoline-fused sugar **2a** in 42% isolated yield, along with rearranged (O-to-N)[13] C1−N-linked oxazoline-fused sugar **2aa** (18%, entry 2). The structure and stereochemistry of oxazoline-fused sugars **2a** and **2aa** were unambiguously confirmed by nuclear magnetic resonance (NMR) techniques (one-dimensional (1D) and two-dimensional (2D) NMR; for details, see the Supporting Information). The newly generated oxazoline-fused sugar is expected to be *cis*-orientation (α−α side), which was strongly supported through the NOE spectrum. The disappearance of methylene multiplet peak (C2−H, δ 3.90−3.89 ppm) and imidic (−NH, δ 8.57 ppm) peak and presence of only singlet peak at δ 6.15 ppm (^{1}H NMR of **2a**), as well as a peak at δ 107.32 ppm (C1) and δ 99.03 ppm (C2) in ^{13}C NMR, confirmed the formation of the *cis*-1,2-fused bicyclic compound. Furthermore, to increase the overall yield of this transformation, various reaction parameters were optimized (for details, see the Supporting Information). Of note, when the combination of NaI/PIDA (3.0 equiv) was employed under the optimized conditions, **2a** was formed exclusively with a slight decrease in the product yield (52%; see Table 1, entry 13). After careful optimization, it can be concluded that employing the mannosylimidate **1a**, NIS (3.0 equiv), Cs_2CO_3 (3.0 equiv) and 24 W blue LED light in CH_2Cl_2 solvent at room temperature (rt) represented the best conditions for the synthesis of oxazoline-fused bicyclic sugar **2a**.

Once the reaction conditions were optimized, we then turned our attention to explore the scope of visible-light-mediated intramolecular β-C−H amination of differentially protected glycosylimidates and a library of oxazoline-fused bicyclic sugars were constructed via a six-membered cyclic transition state (Scheme 2). Therefore, first, we prepared a series of 1,2-*trans* configured diversely protected glycosylimidates (**1a**−**1l**) by following the known literature procedure. Under the optimized conditions, differentially protected mannosylimidates (**1a**−**1d**) afforded the desired oxazoline-fused sugars (**2a**−**2d**) in moderate to good yields (up to 79%). Pleasingly, the reaction condition was tolerant for scale-up synthesis. For example, when the reaction was performed with **1a** at 1.0 mmol scale, the desired oxazoline-fused bicyclic product **2a** was obtained with a slight drop in isolated yield (47%), probably because of the sharply decreased light

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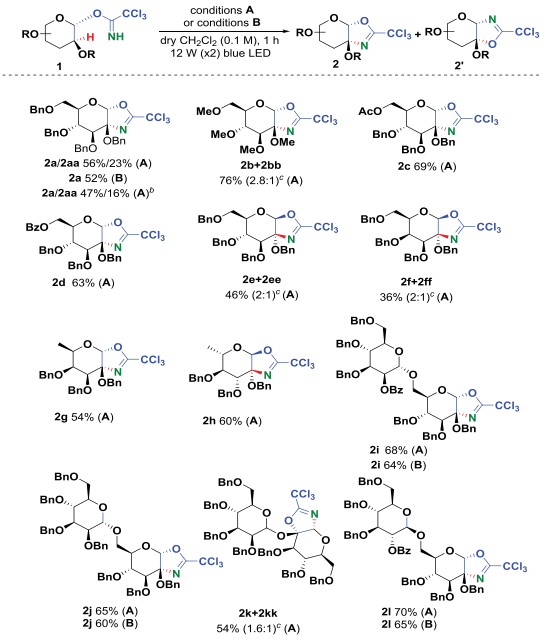
Scheme 2. NCRs-Mediated Synthesis of Oxazoline-Fused Bicyclic Sugars via 1,5-HAT[a]

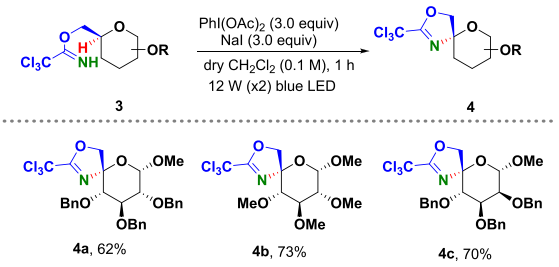


[a]For reaction conditions **A** and **B**, see entries 4 and 13 in Table 1. [b]Reaction was performed at 1.0 mmol scale. [c]The ratio within the parentheses indicates the ratio of **2** and **2′**, not separable through column chromatography.

penetration in the reaction at large scale. Note that when the *trans*-configured *β*-glucosylimidate **1e** and *β*-galactosylimidate **1f** were subjected to the optimized conditions, the desired *β*-C−H amination occurred from the top face (*β*-side) and afforded the C1−O- and C1−N-linked oxazoline-fused bicyclic products (**2e** and **2f**) in moderate yields (46% and 36% (combined yields), respectively). This outcome can be considered to be due to the difference of the stereochemistry at the C-1 and C-2 positions on sugars (hydrogen atom and imidate group are *cis* (top face) to each other). Similarly, 6-deoxy-mannosylimidate **1g** and L-rhamnosylimidates **1h** were also afforded the corresponding C1−O-linked oxazoline-fused products **2g** and **2h** in good yields and with excellent regioselectivity and *cis*-diastereoselectivity. Furthermore, the feasibility of the optimized reactions was also checked with structurally more-complex disaccharide units (**1i**−**1l**). Gratifyingly, the corresponding bicyclic products (**2i**−**2l**) were obtained in good yields under both the conditions **A** and **B**.

Furthermore, we became interested in synthesizing structurally more complexed and conformationally constrained oxazoline-fused spiro sugars via imidate N-radical mediated regioselective *β*-C−H amination through 1,5-HAT. For this purpose, we selected appropriately attached imidates **3**, for instance, C6-linked trichloroacetimidates of glucose and mannose derivatives (**3a**, **3b**, and **3c**) (Scheme 3). Notably, benzyl and methyl protected 6-trichloroacetimidates of glucose and mannose reacted smoothly under condition **B** and gave the corresponding oxazoline-fused spiro bicyclic products (**4a**−**4c**) in good yields (up to 73%). The reaction of three examples showed that the overall transformation proceeds by the activation of *axially* orientated C5−H bonds of the carbohydrate systems through the six-membered cyclic transition state. The structure and stereochemistry of products

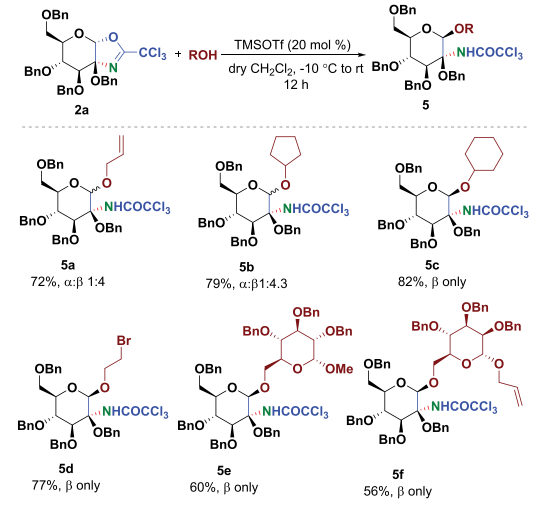
Scheme 3. NCRs-Mediated Synthesis of Oxazoline-Spiro Bicyclic Sugars via 1,5-HAT



were determined from 1D and 2D NMR analyses. For instance, the absence of a C5−H peak and the presence of a C4−H proton as a doublet at δ 3.73 ppm with J = 9.6 Hz in ^{1}H NMR spectrum of compound **4a** confirmed the formation of the oxazoline-fused spiro bicyclic compound (for details, see the Supporting Information). Moreover, the reaction was unsuccessful with C6−O-trichloroacetimidate of galactose **3d** and multiple spots were observed on the TLC plate.

1,2-*cis*-mannosidic linkages are widely present in numerous bioactive natural products and glycoconjugates such as glycoproteins, glycolipids, proteoglycans, microbial polysaccharides, etc.[18] Therefore, several well-documented stereoselective methods are reported in the literature for their syntheses.[19] Hence, we decided to check the synthetic utility of C1−O-linked oxazoline-fused sugars as a novel glycosyl donors to generate 1,2-*cis*-mannosides bearing a quaternary center at C-2 position (see Scheme 4). Thus, oxazoline-fused mannose

Scheme 4. C1−O-Linked-Oxazoline-Fused Sugar Derivatives as a Glycosyl Donor



derivative **2a** was treated with several sugars, and non-sugar-based acceptors in the presence of 20 mol % of TMSOTf and the corresponding mannosides **5a**−**5f** bearing an amino and hydroxyl groups at C-2 positions were obtained in good yields with excellent *β*-selectivity. Disappointingly, when the reactions were performed with less nucleophilic acceptors, such as phenol, thiophenol, amide under optimized conditions, did not give the desired glycosides.

In order to shed some light on the mechanistic aspects of this transformation, several well-designed control experiments were further conducted (Scheme 5). For example, when the

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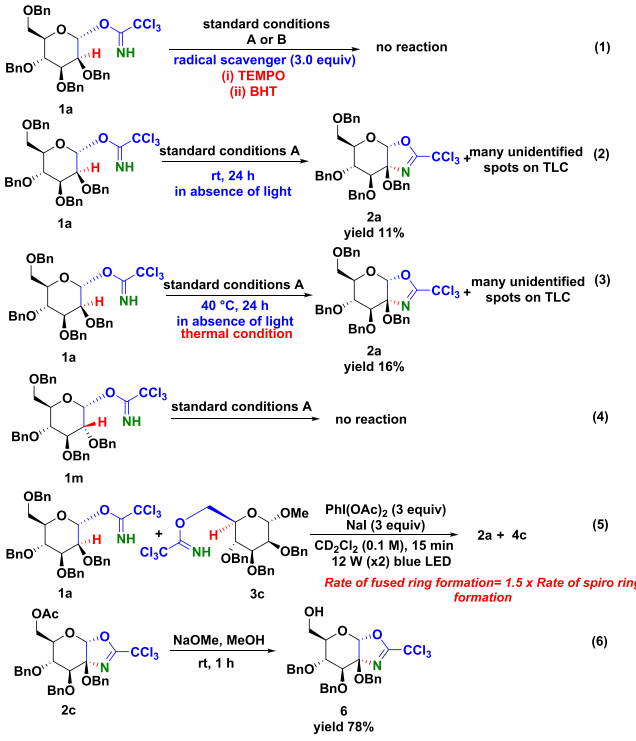
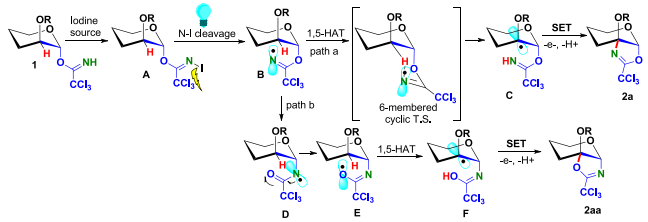
Scheme 5. Control Experiments



reaction was performed in the presence of radical quenchers, such as TEMPO and BHT, under the standard conditions, no product was formed, and the result indicates that the reaction apparently proceeds through the radical mechanism (Scheme 5, entry 1). Indeed, control experiments (in the absence of visible-light; see Scheme 5, entries 2 and 3) illustrate the significance of light in this transformation. Only a meager yield of product **2a** was obtained (11% and 16%, respectively) with several uncharacterized products. To demonstrate the appropriate stereochemical requirements of glycosylimidate for the successful activation of β-C−H bond of carbohydrates, we performed another setup of reaction with α-glucopyanosylimidate **1m**, where imidate (−NH) and H atom are *trans* to each other under standard conditions (Scheme 5, entry 4). Interestingly, no desired product was formed, which eventually support that oxazoline moiety fused to sugar template via *cis*-orientation. Notably, we performed the intermolecular competition reaction between the equimolar amount of mannosyl-1-imidate **1a** and mannosyl-6-imidate **3c** under the given conditions **B** to compare the rate of formation of fused versus spiro bicyclic sugars via 1,5-HAT (Scheme 5, entry 5). The observed results (based on ^{1}H NMR analysis; for details, see the Supporting Information) suggests that the formation of oxazoline-fused bicyclic sugar **2a** is slightly favorable over the oxazoline-fused spiro sugar **4c**. On the other hand, the stability of oxazoline-fused sugar **2c** was further checked under basic conditions. Impressively, there was no harm on fused ring junction and acetyl group cleaved to give the corresponding product **6** in 78% yield (Scheme 5, entry 6).

On the basis of control experiments and literature reports,[13,14] a plausible reaction mechanism for NCRs triggered β-C−H amination of glycosylimidates via visible-light-induced 1,5-HAT is depicted in Scheme 6. Initially, NIS or NaI/PIDA reacts with glycosylimidate **1** to give N-iodo-imidate species **A**. Upon photoirradiation, the N-iodo-species

Scheme 6. Anticipated Mechanism



undergoes homolytic cleavage to give N-centered radical **B**. Then, N-radical abstracts appropriately positioned H atom via thermodynamically favorable six-membered-cyclic transition state to produce C-centered radical **C** (path a). Subsequently, species **C** loses the single-electron to generate carbocation, followed by intramolecular cyclization to form N−C bond and eventually generate a quaternary center at the C-2 position. The desired C1−O-linked oxazoline-fused sugar derivatives **2a** are obtained after final deprotonation. For the formation of minor isomer (C1−N-linked) oxazoline-fused sugar derivative **2aa**, we believe that the reaction would have initiated via the rearrangement of iminyl radical **B** to amidyl radical **D** (O- to N-rearrangement)[13] under visible-light conditions (path b).[13] Consequently, amidyl radical **D** undergoes rearrangement to generate *O*-centered radical **E**. Then, the *O*-centered radical abstract H atom from appropriately positioned methylene carbon via 1,5-HAT to generate C-radical **F**, followed by SET, furnishes the carbocation intermediate, which finally undergoes for intramolecular cyclization to form C2−O bond and produces the minor regioisomer C1−N linked oxazoline-fused sugar **2aa**.

In summary, we have developed a diastereoselective approach for the synthesis of oxazoline-fused and spiro bicyclic sugars under metal-free conditions using NIS/Cs_2CO_3 or NaI/PIDA as a reagent system and visible light as the source of energy. The designed strategy proceeds via selective β-C(sp^3)−H activation of an appropriately positioned glycosylimidate substrates to form N−C bond through 1,5-HAT from transient imidate N-radicals. This method conveniently introduces the oxazoline moiety on sugar templates in a stereocontrolled fashion and generates a quaternary center at the C-2/C-5 positions. Furthermore, conformationally constrained oxazoline-fused bicyclic sugars were employed as an efficient glycosyl donor for the synthesis of C-2 functionalized β-mannosides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00763.

Detailed experimental procedures and ^{1}H, ^{13}C, COSY, and HSQC NMR and HRMS data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Prof. Vinod. K. Singh (Department of Chemistry, IIT Kanpur) on the occasion of his 60th birthday.

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