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# Construction of Fused Oxabicyclic Scaffolds from Glycals and Styrenes via One-Pot Domino Transformations

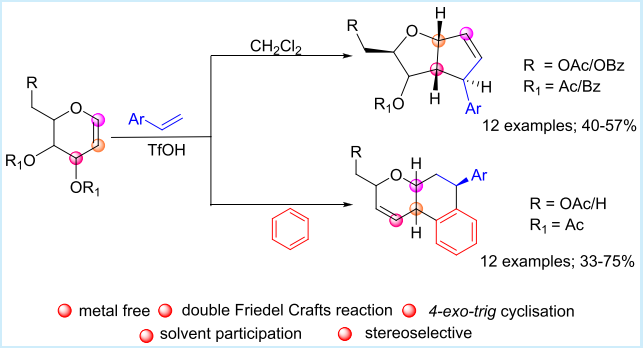
Monika Bhardwaj,[†,§] Faheem Rasool,[†,‡,§] Madhu Babu Tatina,[†] and Debaraj Mukherjee*[,†,‡]

[†]Natural Product Chemistry Division, Indian Institute of Integrative Medicine (IIIM), Jammu 180001, India

[‡]Academy of Scientific and Innovative Research (AcSIR-IIIM), Jammu 180001, India

Supporting Information

**ABSTRACT:** Triflic acid catalyzed cascade stereoselective reaction of glycals with styrenes delivers complex oxabicyclic scaffolds such as *cis*-oxadecalins or *cis*-cyclopentanofurans simply by tweaking the solvent. In the presence of participating solvents like benzene/toluene, cascade Ferrier *C*-glycosylation and double Friedel−Crafts reaction leads to densely chiral benzo-fused oxadecalins, whereas in DCM, an unprecedented ring-opening, ring-closing sequence generated *cis*-cyclopentanofurans. An attempt has been made to explain the above cascade sequences via intermediate trapping, kinetic experiments, and Baldwin's rules.

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Creation of molecular complexity from common starting materials with high efficiency maintaining stereochemical integrity and in minimum synthetic steps while adhering to economic and environmental considerations constitutes a great challenge in modern organic synthesis which can be addressed by domino reactions.[1−3] However, doing these types of consecutive stereoselective reactions in densely functionalized substrates like carbohydrates poses a challenge. For example, glycals are cheap and stable carbohydrate-based enol ethers used extensively in the synthesis of biologically important complex molecules,[4] but these have been employed in only few cascade reactions.[5] During the past several years we have been involved in the development of new domino reactions of glycals leading to the synthesis of substituted furfuryl derivatives,[5a] vinyl-*C*-glycosides[5c] and *α,β,γ,δ*-conjugated chirons[5d] using different Lewis acid catalysts. In the present paper, we would like to disclose unprecedented domino reactions of glycals (**I**) with styrenes to generate fused chiral oxabicyclic scaffolds, namely, chiral cyclopenta[*b*]furans (**II**) and oxadecalins (**III**) by altering the solvents (Scheme 1a). It is pertinent to mention here that oxabicycles serve as the structural core for a diverse variety of natural products and bioactive molecules. For example, *cis*-fused 1-oxadecalins and cyclopenta[*b*]furans are ubiquitously present in bioactive natural products[6] like Phomactine A, Koninginin, Communiol E, and Communiol F having different biological activities[7] (Scheme 1b). Because of their complexity and presence of multiple stereocenters, stereocontrolled routes to such scaffolds are always desirable.

The idea stems from our earlier observation in which less reactive nucleophiles such as unactivated alkynes were observed to form C−C bond at the anomeric center of glycals under Lewis acid conditions.[5f] This prompted us to investigate whether weak nucleophiles like styrene can attack the anomeric carbon of glycal in the presence of Lewis acids and to find out the fate of the benzylic carbocation (**A**) thus generated (Scheme 1a). Toward this goal, we commenced our study with tri-*O*-acetyl-D-glucal (**1**) and 4-methylstyrene as model substrates in the presence of various Lewis acids and solvents at different temperatures. This showed that the nature of the Lewis acid played a significant role on the fate of the reaction. For example, in the presence of halogenated Lewis acids such as $FeCl_3$ or $FeBr_3$, the benzylic carbocation formed after initial attack on anomeric carbon by styrene was trapped by the halide nucleophile to produce **3** and **4** (Table 1, entries 1 and 2), respectively, as the only products but as diastereomeric mixtures. To avoid the use of halogenated Lewis acids, TfOH was used. With 0.2 equiv of TfOH at −30 °C (Table 1, entry 3), we observed the formation of a UV-inactive anomeric hydroxyl carbohydrate product **6** without attachment of styrene. Increasing the proportion of TfOH as well as temperature (Table 1, entry 4) led to the formation of products **5** and **6**. Further increase of the reaction temperature to 0 °C (Table 1, entry 5), surprisingly, revealed the formation of a new product **2** with a decrease in the yield of **5**. Detailed 2D NMR analysis revealed the structure **2**, an unexpected cyclopenta[*b*]furan derivative. It suggested the linkage of styrene to the anomeric carbon of glucal. Strong correlation between H1−H6 and H2−H8 signals in 1H−1H COSY of **2** (see Figure 1 in the SI) confirmed their adjacent nature. The stereochemistry of compound **2** was determined by 2D-

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**Scheme 1. (a) Present Work on the Generation of Oxabicyclic Cores from Glycals and Styrenes in Different Solvents. (b) Natural Products Containing Oxabicyclic Rings**

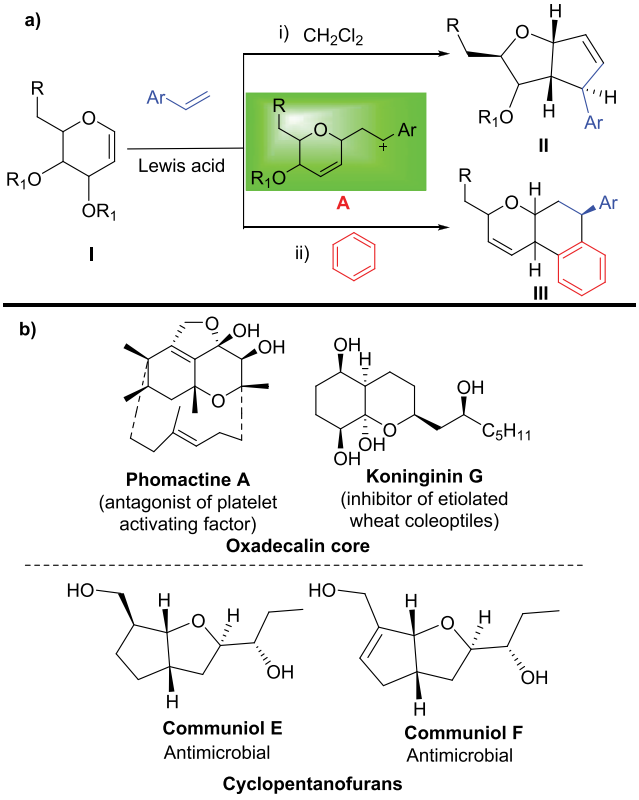
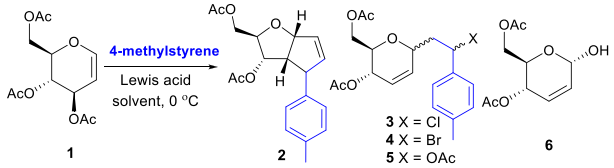



**Table 1. Reaction of Tri-*O*-acetyl-D-glucal with Styrene under Various Lewis Acid Conditions**[a]

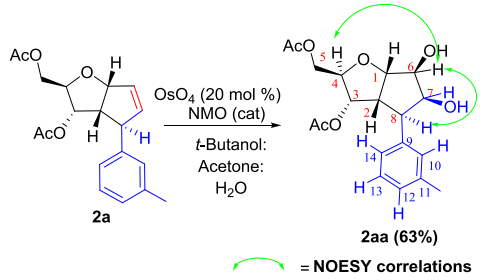



| entry | Lewis acid (equiv) | temp (°C) | time (h) | product | yield (%) |
|---|---|---|---|---|---|
| 1 | $FeCl_3$ (1) | 0 | 1 | **3** | 55 |
| 2 | $FeBr_3$ (1) | 0 | 1 | **4** | 62 |
| 3 | TfOH (0.2) | −30 | 1 | **6** | 60 |
| 4 | TfOH (0.5) | −10 | 0.5 | **5:6** | 55:10 |
| 5 | TfOH (0.5) | 0 | 0.5 | **2:5** | 15:45 |
| 6 | TfOH (1) | 0 | 0.5 | **2:5** | 35:25 |
| 7 | TfOH (2) | 0 | 0.5 | **2:5** | 50:20 |
| 8 | TfOH (1) | rt | 0.5 | ND | |
| 9 | TMSOTf (1) | 0 | 0.5 | **2:5:6** | 20:20:10 |
| 10 | $BF_3{\cdot}Et_2O$ (1) | 0 | 1 | **6** | 20 |
| 11 | $Cu(OTf)_2$ (1) | 0 | 1 | ND | |

[a]Reactions were carried out using **1** (1 equiv) and 4-methylstyrene (1 equiv) in 3 mL of dichloromethane.

NOESY (see Figure 1 in the SI). The coupling constant of 5.5 Hz for an alkene proton confirms cyclopentene moiety.[8] Finally, in order to find out the position of double bond in cyclopenta[*b*]furan moiety we have conducted syn dihydroxylation by $OsO_4$–NMO of derivative **2a** (Scheme 2) derived from 3-methylstyrene and glucal triacetate and predictably dihydroxylation occurred via attack at the less hindered $\beta$-face.

**Scheme 2. Syn Dihydroxylation of Chiral Cyclopenta[*b*]furan 2a**




In order to enhance the yield of the cyclopenta[*b*]furan product, we increased the concentration TfOH (Table 1, entries 6 and 7) and screened other Lewis acids (Table 1, entries 9–11). Summarizing the outcome of our optimization study, the use of 2 equiv of TfOH at 0 °C in DCM (Table 1, entry 7) proved to be the best condition for the formation of cyclopenta[*b*]furan **2**.

The substrate scope of the new reaction was examined by using various substituted styrenes and glycals resulting in the formation of the expected products in moderate yield with high stereoselectivity (Scheme 3). Styrenes possessing either electron-donating (Scheme 3, entries **2a** and **2b**) or -withdrawing (Scheme 3, entries **2d–2j**) groups undergo similar type of conversion generating various cyclopenta[*b*]furan scaffolds, but those with EDGs ensured somewhat better yields. Moreover, no reaction occurs in the case of highly electron-deficient styrenes like 4-cyano- and 4-nitrostyrenes, whereas $\alpha$-methylstyrene gives a complex mixture of products which could not be resolved. A series of other glycals were also examined under the standard reaction conditions.

We also investigated the role of aromatic solvents which may participate in the above transformation to trap the benzylic carbocation initially generated from the glycosylation of styrene with glycals and thereby initiate a new kind of cascade reaction (Scheme 1a, path ii). Thus, we carried out the reaction of tri-*O*-acetyl-D-glucal (**1**) with styrene in the presence of TfOH (2 equiv) at 0 °C in benzene (Table 2, entry 1). A new product different from **2** was obtained and characterized as compound **7** by extensive NMR analysis and mass spectroscopy (see the SI). The oxadecalin ring fusion must be *cis* ($J$ = 5.7 Hz), as a *trans*-fused ring will have both the ring juncture protons axially oriented showing higher coupling constant. Various non-nucleophilic Lewis acids in different proportions were then screened under different conditions (Table 2). The temperature and amount of TfOH played a very important role on the yield of the reaction. From the optimization study, addition of 30 mol % of TfOH at 0 °C to a solution of tri-*O*-acetyl-D-glucal (1 equiv) and styrene (1 equiv) in benzene followed by the stirring of the reaction mixture at 40 °C for 2 h were found to be the best conditions (SI, Table 2, entry 8).

The substrate scope of the new cascade reaction was expanded by taking various substituted styrenes with tri-*O*-acetyl-D-glucal (**1**) in aromatic solvents like benzene and toluene to get the products in good yields (Scheme 4). In the case of symmetrically substituted diaryl compounds, only one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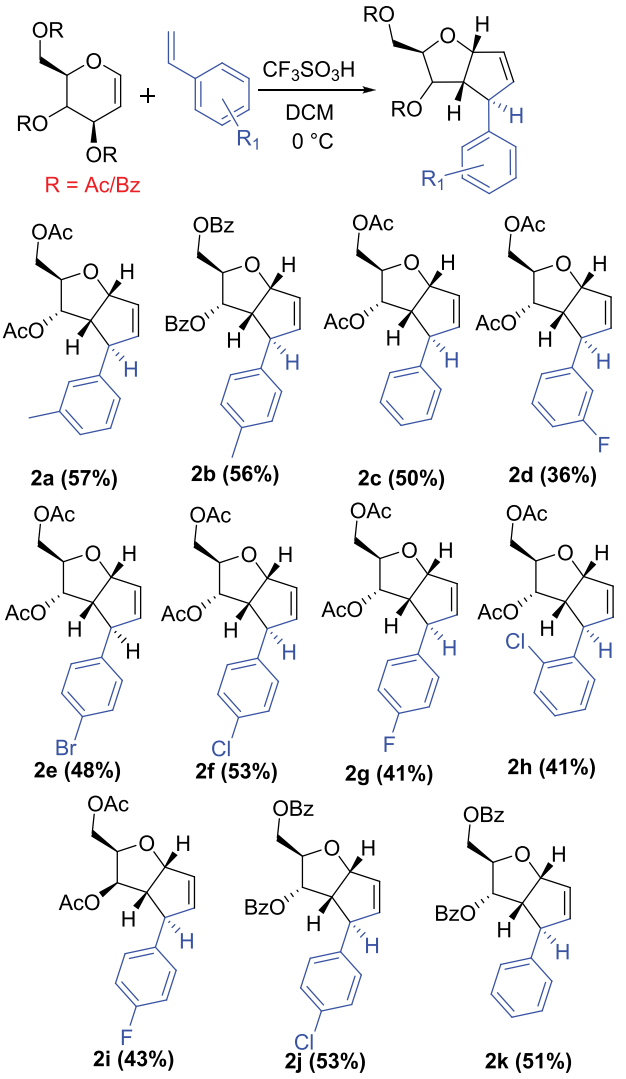
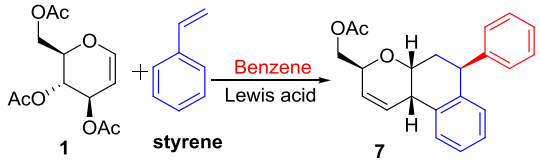
**Scheme 3. Substrate Scope of the Reaction of Glycals with Various Styrenes in Dichloromethane under Optimized Reaction Conditions**[a]




[a]Reactions were carried out by using glycal (1 equiv), styrene (1 equiv), and TfOH (2 equiv) in 3 mL of $CH_2Cl_2$ at 0 °C for 30 min.

product was observed (Scheme 4, entries **7e** and **7f**). In the case of unsymmetrically substituted diaryl products, a mixture of two inseparable regioisomers was obtained (Scheme 4, entries **7d** and **7h**−**7k**). Although four regioisomers are possible in the case of products formed from unsymmetrically substituted intermediates (taking into account the possibility of o/p substitution in the intermolecular reaction), only two regioisomeric products were formed in most of the cases as confirmed by $^1$H NMR (Scheme 4, entries **7a**, **7d**, **7h**−**7k**). Interestingly, with 2-substituted styrenes (except 2-bromostyrene in benzene), only single products were found, with either the aryl ring of styrene or the solvent participating in the second Friedel−Crafts reaction (Scheme 4, entries **7b**, **7c**, and **7g**). Regioselectivity of the reaction was determined from the HMBC (see the SI). Fortunately, when 2-bromostyrene was reacted in benzene with tri-*O*-acetyl-D-glucal, we were able to isolate both the regioisomers in a 5:1 ratio, the major one being the product where solvent took part in a second Friedel−Crafts alkylation (Scheme 4, entries **7a** and **7a′**).

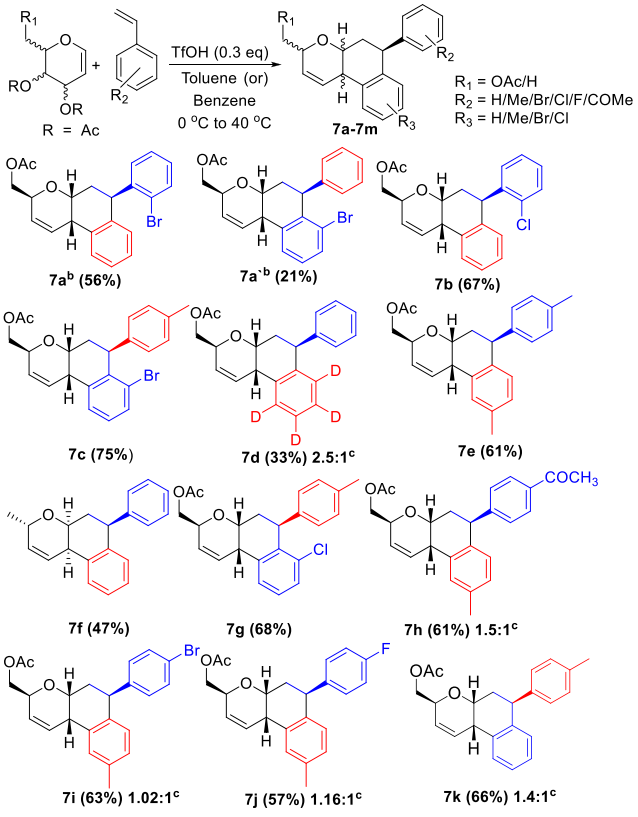
**Table 2. Reaction of Tri-*O*-acetyl-D-glucal with Styrene in Benzene**[a]




| entry | Lewis acid (equiv) | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|
| 1 | TfOH (2) | 0 | 4 | 40 |
| 2 | TMSOTf (1) | 0 | 4 | 30 |
| 3 | ZnOTf (1) | 0 | 0.25 | ND |
| 4 | CuOTf (1) | 0 | 0.25 | ND |
| 5 | $BF_3.Et_2O$ (1) | 0 | 0.25 | ND |
| 6 | TfOH (0.5) | 0 | 5 | 45 |
| 7 | TfOH (0.1) | rt | 2 | 40 |
| 8[b] | TfOH (0.3) | 0−40 | 2 | 73 |

[a]Reactions were carried out using tri-*O*-acetyl-D-glucal (1 equiv) and styrene (1 equiv) in 3 mL of benzene to which TfOH was added. [b]Addition of TfOH to a solution of glucal (1 equiv) and styrene (1 equiv) in benzene was done at 0 °C, then the reaction was stirred at 40 °C.

**Scheme 4. Substrate Scope of the Reaction of Glycals with Various Styrenes in Nucleophilic Solvents (Benzene and Toluene) under Optimized Reaction Conditions**[a]




[a]Glycal (1 equiv), styrene (1 equiv), TfOH (30 mol %), solvent (3 mL). [b]Both regioisomers were separated and characterized. [c]Only structures of major regioisomers were shown, and ratios were determined from crude $^1$H NMR.

Since there is no literature precedent on these types of cascade reactions, we wanted to gain some insight into the



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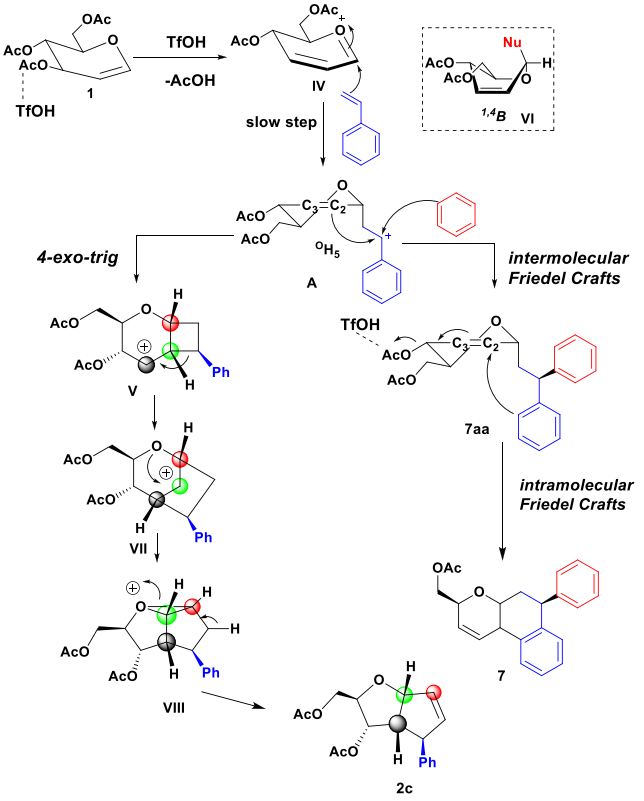
plausible mechanism by performing control and isotope-labeling experiments. It is evident that the reaction starts with initial protonation of the glucal to form oxocarbenium ion **IV** (Scheme 5) followed by attack of styrene at the anomeric

**Scheme 5. Plausible Mechanism for the Formation of the Oxadecalins/Cyclopenta[*b*]furans from Glycals and Styrene**[a]




[a]Mechanism of formation of **2c** and **7** from **1**.

carbon from the $\alpha$-side leading to the formation of a stable $^{O}H_5$ benzyl carbocation **A**. The attack of the styrene from the $\beta$-side leads to the formation of a less stable $^{1,4}B$ boat conformation **VI**, making it less feasible. Intermediate **A** possibly undergoes intramolecular cyclization following a 4-*exo-trig* process, favored under Baldwin's rules of cyclization forming **V**. Subsequent 1,2-shift then leads to the formation of carbocation **VII**, which is stabilized by the neighboring oxygen atom to form oxiranyl cation **VIII**. Ring opening of the oxiranyl cation with deprotonation gives cyclopenta[*b*]furan product **2c**.

In presence of an external nucleophile like benzene, the intermediate **A** is likely to undergo double displacement via two consecutive Friedel–Crafts alkylation reactions to give the oxadecalin core. In order to explain this, we carried out the reaction of tri-*O*-acetyl-D-glucal with styrene at 0 °C in benzene using 10 mol % of TfOH and quenched the reaction at short intervals (after 15 min) to trap the likely intermediate **A**. Indeed, we obtained a new product **7aa** via Friedel–Crafts alkylation of benzene with the carbocation **A**. Further reaction of **7aa** in the presence of TfOH at 40 °C via Friedel–Crafts alkylation of the diphenyl derivative with the C-2 carbocation of the pyran ring derived from the second acetyl elimination ends up in the cyclized product **7** (Figure 1i). At this stage, chemoselectivity is determined. In the case of unsymmetrically

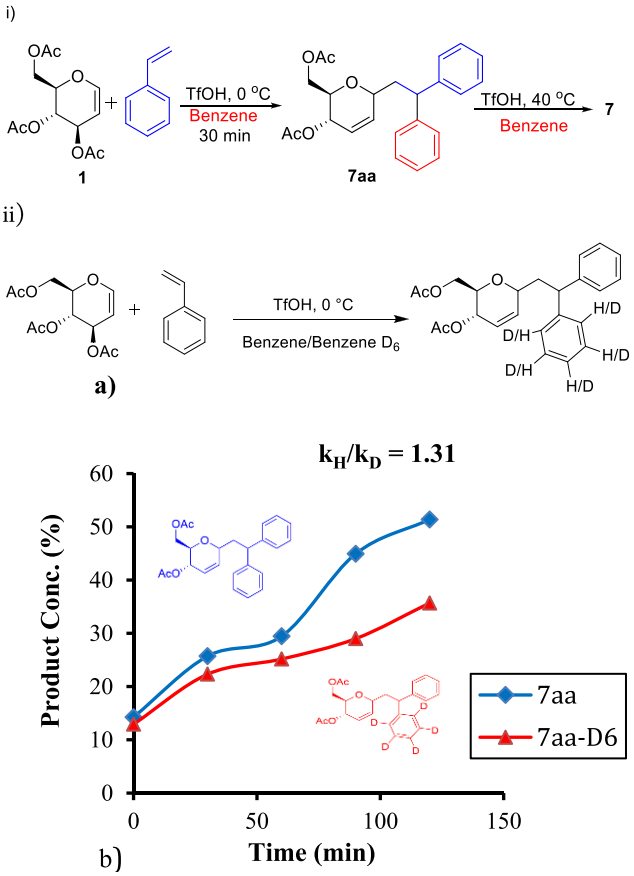



**Figure 1.** (i) Reaction of tri-*O*-acetyl-D-glucal and styrene with temperature variation. (ii) Isotopic-labeling experiments: (a) reaction with normal benzene and deuterated benzene, (b) KIE plot. *Reaction monitoring by HPLC using 0.1% formic acid in water (A) and acetonitrile (B) in gradient, temp 35 °C, flow rate 1 mL/min, at wavelength 210 nm in Column LiChrospher C18, 250 mm × 5 $\mu$m.

disubstituted diphenyl derivatives, two regioisomers may be observed depending upon which ring takes part in the second Friedel–Crafts reaction controlled by cumulative effects of activation or deactivation exerted by each substituent.

In addition we have carried out isotope labeling experiment to find out the slowest step of these cascade reactions. For that purpose, we installed two set of reactions in which glucal triacetate and styrene were allowed to react in the presence of normal benzene and deuterated benzene at 0 °C with the addition of 0.03 mol % of TfOH at 30 min time intervals and monitored it through HPLC up to 120 min. The $k_H/k_D$ value of 1.31 determined from the absolute rates of two set of reactions showed that the glycosylation step is the slowest step (Figure 1ii).

In conclusion, we have developed two new cascade reactions in which bicyclic *cis*-fused oxabicylic scaffolds, namely, benzannulated oxadecalins and cyclopenta[*b*]furans, were synthesized from glycals and styrenes in a highly stereoselective fashion. The solvent played a major role in the outcome of the reaction. Only TfOH has been used as a catalyst to obtain such complex scaffolds without activation of any of the starting materials. Isotope-labeling studies reveal that glycosylation is the slowest step of the reaction sequence. These metal-free domino reactions have allowed a fundamentally new type of transformation to be discovered that has significant potential in chemistry and chemical biology.



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## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00234.

Experimental procedures, $^{1}H$ and $^{13}C$ NMR spectra, and characterization of all compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: dmukherjee@iiim.ac.in.

### ORCID

Debaraj Mukherjee: 0000-0002-2162-7465


### Author Contributions

§M.B. and F.R. contributed equally.

### Notes

The authors declare no competing financial interest.

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