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The first examples of cyclizations of a glycal with enamines leading to oxa-aza bicyclononene scaffolds

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Abstract—Glycals undergo smooth coupling with β-enaminoketones and β-enaminoesters generated in situ from 1,3-dicarbonyl compounds and arylamines in the presence of 10 mol % of $InCl_3$ in refluxing dichloroethane to produce oxa-aza bicyclononene scaffolds in excellent yields with high selectivity. The use of $InCl_3$ makes this protocol simple, convenient and easy to scale-up.

The ready availability of a wide range of carbohydrates in nature and their multi-chiral architecture, coupled with their well-defined stereochemistry, make them attractive starting materials in organic synthesis.[1,2] In particular, glycals (1,5-anhydro-hex-1-enitols), that is, 1,2-unsaturated derivatives of pentoses and hexoses are among the most versatile chiral building blocks.[3] They are ambident electrophiles capable of reacting with various nucleophiles under the influence of acid catalysts or oxidants to produce 2,3-unsaturated glycosides.[4] They are very useful precursors in oligosaccharide synthesis.[5] Recently, multicomponent one-pot synthesis has received attention because of its wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery.[6]

In this Letter, we report a versatile approach via a three-component coupling (3CC) involving the condensation of glycals, 1,3-dicarbonyl compounds and arylamines. The 3CC reaction was carried out in the presence of an acid catalyst, usually 10 mol % of indium(III) chloride. This robust approach allows for the preparation of a diverse range of products and suited our requirements in continuation of a synthetic program aimed at the generation of combinatorial libraries for drug discovery. Initially, we studied the three-component coupling of tri-*O*-acetyl-D-glucal, acetylacetone, and aniline using 10 mol % indium(III) chloride as a novel glycosyl activator. The unusual bicyclic adduct **4a** was isolated in 93% yield with high stereoselectivity (Scheme 1).

Product **4a** was characterized thoroughly with the help of various NMR experiments including extensive ^1H decoupling, 2-D nuclear Overhauser effect spectroscopy (NOESY), heteronuclear single-quantum correlation spectroscopy (HSQC), and heteronuclear multiple bond correlation spectroscopy (HMBC). The NMR data suggest that the molecular structure of **4a** consists of a [2.3.3]bicyclononene-like structure. The location of the methylene group in the bridge of the bicyclononene-like structure was confirmed by small couplings with the bridgehead protons H1 and H3 ($j_{H1-H2_{(pro\text{-}S)}} = 3.0$ Hz, $J_{H1-H2_{(pro\text{-}R)}} = 2.2$ Hz, $J_{H2_{(pro\text{-}S)}-H3} = 3.0$ Hz, and $J_{H2_{(pro\text{-}S)}-H3} = 4.3$ Hz; Fig. 1). The two six-membered rings of the bicyclononene moiety differ in their conformations. For the pyranose ring, $J_{H4-H5} = 10.3$ Hz and the NOESY cross peak $H2_{(pro\text{-}S)}/H4$ supports the $^4C_1$chair form. NOE correlations, $H5/H_{ortho}$ and $H1/H_{ortho}$ further confirm that the *N*-Ph group is on the same side as the ring oxygen, while the location of the methyl group adjacent to the ring nitrogen was amply supported by NOE, $C11/H_{ortho}$. Additionally, HMBC correlations, H4/C13, H3/C12 and H1/C12 were in complete agreement with the proposed structure.

Keywords: Glycals; 1,3-Dicarbonyls; Indium compounds; Oxa-aza-heterobicycles.
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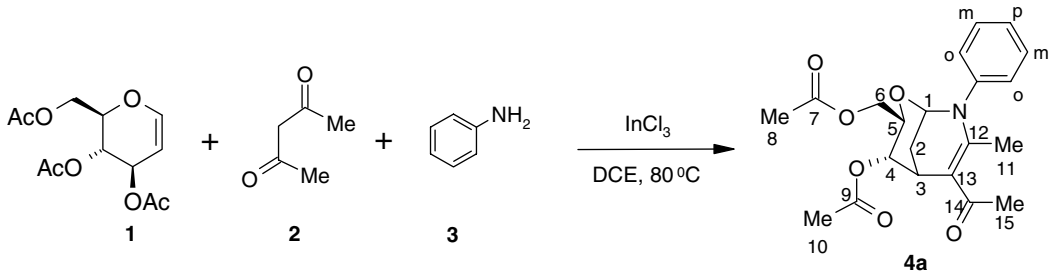


Scheme 1.

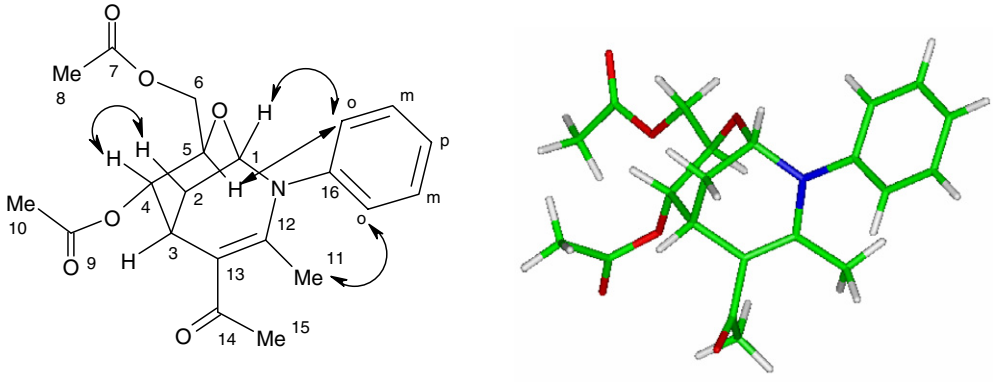


Figure 1. Characteristic NOE interactions and the energy-minimized structure of **4a**.

Interestingly, the structure differs from that expected from our earlier studies on glycals.[7] Further, the energy-minimized structure of **4a** was obtained from molecular mechanics calculations and is shown in Figure 1.[8]

This unexpected result prompted us to apply this process to various glycals, 1,3-dicarbonyl compounds, and arylamines. Substituted arylamines such as *p*-toludine, *p*-anisidine, *p*-chloroaniline, *p*-fluoroaniline, 3,4-methylenedioxyaniline, *o*-toludine, and 1-naphthylamine participated in this reaction to produce the corresponding heterobicycles in good yields (Table 1). Other glucal derivatives including 3,4,6-tri-*O*-methyl- and 3,4,6-tri-*O*-allyl-D-glucal reacted efficiently with enamines generated in situ from 1,3-diones and arylamines to produce cyclic adducts (Table 1). Besides acetylacetone, methyl

Table 1. $InCl_3$-catalyzed three-component coupling of glycals, 1,3-diones and aryl amines

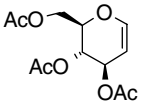
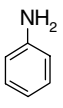
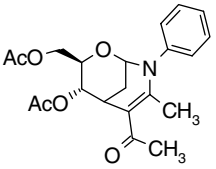
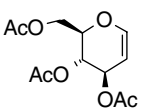
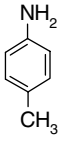
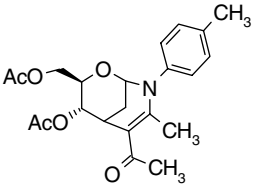
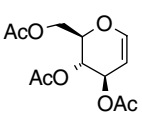
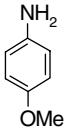
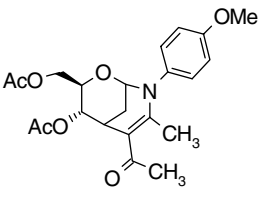
Entry	Glycal	Amine	1,3-Dione	Product[a]	Reaction time (h)	Yield[b] (%)
a			Pentane-2,4-dione		5.0	93
b			Pentane-2,4-dione		6.0	85
c			Pentane-2,4-dione		5.0	91

Table 1 (*continued*)

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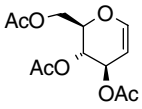
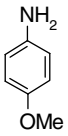
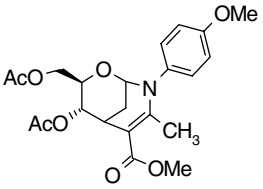
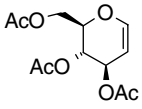
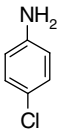
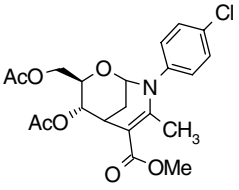
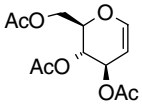
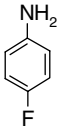
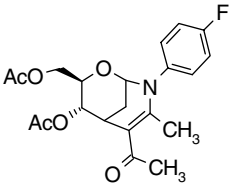
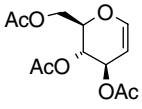
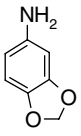
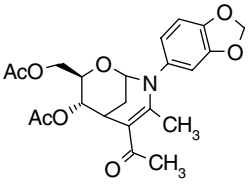
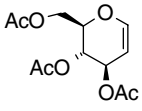
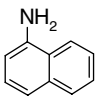
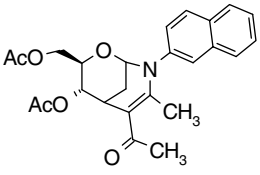
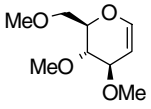
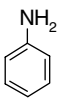
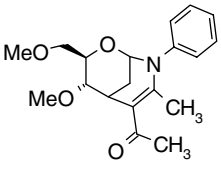
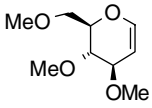
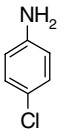
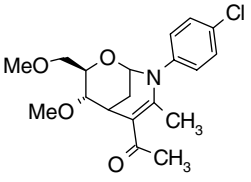
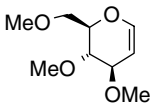
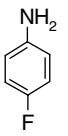
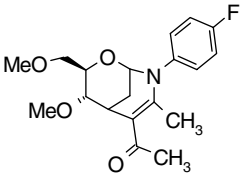
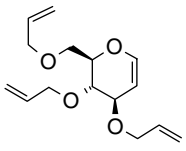
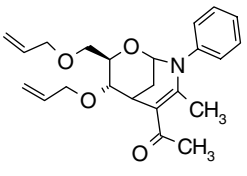
d			Methyl acetoacetate		6.0	85
e			Methyl acetoacetate		5.5	83
f			Pentane-2,4-dione		5.5	85
g			Pentane-2,4-dione		5.0	87
h			Pentane-2,4-dione		6.0	75
i			Pentane-2,4-dione		6.0	85
j			Pentane-2,4-dione		6.0	87
k			Pentane-2,4-dione		6.0	82
l			Pentane-2,4-dione		5.5	90

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Table 1 (*continued*)

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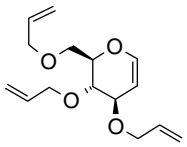
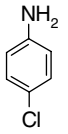
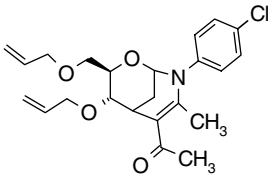
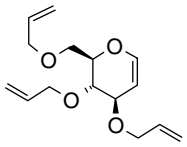
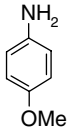
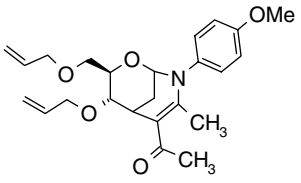
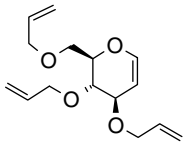
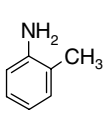
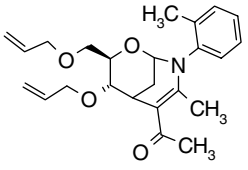
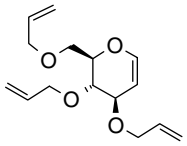
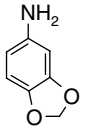
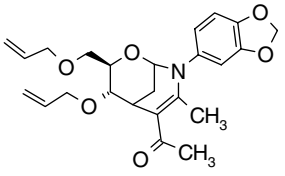
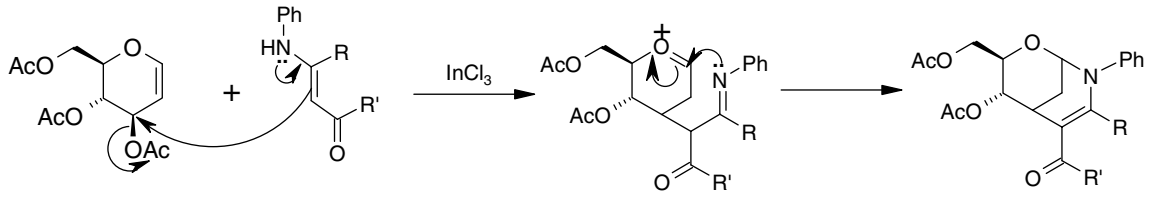
m			Pentane-2,4-dione		6.0	81
n			Pentane-2,4-dione		6.0	85
o			Pentane-2,4-dione		5.5	83
p			Pentane-2,4-dione		6.0	89

[a] All products were characterized by NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 2.

acetoacetate also participated in this reaction. A plausible mechanism for the formation of products **4** is depicted in Scheme 2.

This method is a highly stereoselective, one-pot synthesis of unusual bicyclic heterocycles under mild conditions. The efficacy of various Lewis acids such as $InCl_3$, $BiCl_3$, $CeCl_3{\cdot}7H_2O$, YCl_3, and $YbCl_3$ was tested. Indium trichloride was found to be the most effective catalyst in terms of conversion and selectivity. For instance, treatment of tri-*O*-acetyl-D-glucal with acetylacetone and aniline in the presence of 10 mol % $InCl_3$, 10 mol % $BiCl_3$, and 10 mol % $CeCl_3{\cdot}7H_2O$ for 5 h afforded **4a** in yields of 93%, 78%, and 65%, respectively. Alternatively, 10 mol % of $InBr_3$ was found to be equally effective for this conversion. However, in the absence of either $InCl_3$ or $InBr_3$, the reaction did not proceed even after an extended time. Various triflates were also screened including $In(OTf)_3$, $Sc(OTf)_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Dy(OTf)_3$, and $Sm(OTf)_3$ but none of them gave satisfactory yields. Simple cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran afforded the corresponding tetrahydroquinoline derivatives under similar reaction conditions.[9] Furthermore, the reaction also proceeded with protic acids, specifically montmorillonite KSF or PMA/SiO_2, at 80 °C in 1,2-dichloroethane to yield the same products.

In conclusion, we have disclosed a three-component, one-pot synthesis of novel carbohydrate derivatives, oxa-aza-heterobicycles, from glycals, 1,3-dicarbonyls, and aryl amines using a catalytic amount of indium trichloride under mild conditions.[10] This is an entirely new approach to functionalize glycals with 1,3-dicarbonyl compounds and arylamines, leading to oxa-aza bicyclononene scaffolds.

Acknowledgments

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10. *Experimental procedure*: A mixture of glucal triacetate (272 mg, 1 mmol), aniline (103 mg, 1.1 mmol), pentane-2,4-dione (110 mg, 1.1 mmol), and $InCl_3$ (0.1 mmol) in dichloroethane (10 mL) was heated at 80 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with water followed by brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on a silica gel column using a mixture of ethyl acetate: *n*-hexane (3:7) afforded pure product.

Spectral data for selected products: Compound **4a**: Colorless solid, mp 122–123 °C. IR (KBr): ν_{max} 2924, 2832, 1731, 1705, 1643, 1530, 1490, 1414, 1385, 1291, 1215, 1120, 1093, 1066, 1018, 981, 831, 721, 599, 553, 507 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (t, $J = 7.7$ Hz, 2H, *meta*), 7.32 (t, $J = 7.1$ Hz, 1H, *para*), 7.19 (d, $J = 7.9$ Hz, 2H, *ortho*), 5.01 (m, 1H, H1), 4.92 (dd, $J = 4.3$, 10.3 Hz, 1H, H4), 4.17 (dd, $J = 5.6$, 11.9 Hz, 1H, H6), 4.07 (dd, $J = 2.5$, 11.9 Hz, 1H, H6′), 3.83 (ddd, $J = 2.5$, 5.6, 10.4 Hz, 1H, H5), 3.59 (m, 1H, H3), 2.27 (dt, $J = 3.0$, 12.8 Hz, 1H, $H2_{(pro\text{-}S)}$), 2.22 (s, 3H, 15-Me), 2.15 (s, 3H, 11-Me), 2.06 (s, 3H, 8-Me), 2.04 (s, 3H, 10-Me), 1.92 (ddd, $J = 2.2$, 4.3, 12.8 Hz, 1H, $H2_{(pro\text{-}R)}$). ^{13}C NMR (proton decoupled, 150 MHz, $CDCl_3$): $\delta = 197.3$ (C14), 170.8 (C7), 170.3 (C9), 154.3 (C12), 143.4 (C16), 129.5 (*meta*), 128.2 (*ortho*), 127.8 (*para*), 108.1 (C13), 82.4 (C1), 70.9 (C4), 68.4 (C5), 63.2 (C6), 30.5 (C3), 30.1 (C15), 28.4 (C2), 21.1 (C10), 20.45 (C11), 20.0 (C8). LCMSD: *m/z*: (M^++H) 388. HRMS calcd for $C_{21}H_{26}NO_6$ (M^++H): 388.1760, found, 388.1756.

Compound **4j**: Pale yellow liquid, IR (KBr): ν_{max} 2929, 2827, 1701, 1640, 1530, 1490, 1383, 1293, 1213, 1120, 1093, 1065, 1013, 989, 831, 722, 599, 570 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, $J = 8.6$ Hz, 2H), 7.05 (d, $J = 8.6$ Hz, 2H), 4.95 (m, 1H), 3.52 (dd, $J = 4.3$, 10.3 Hz, 1H), 3.49 (dd, $J = 5.6$, 11.9 Hz, 1H), 3.45 (dd, $J = 2.5$, 11.9 Hz, 1H), 3.40 (ddd, $J = 2.5$, 5.6, 10.4 Hz, 1H), 3.38 (m, 1H), 3.41 (s, 3H), 3.35 (s, 3H), 2.21 (s, 3H), 2.09 (dt, $J = 3.0$, 12.8 Hz, 1H), 2.01 (s, 3H), 1.80 (ddd, $J = 2.2$, 4.3, 12.8 Hz, 1H).^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 198.2, 152.5, 142.2, 133.0, 129.6, 129.5, 109.7, 82.5, 78.5, 71.5, 59.2, 58.3, 31.8, 30.3, 29.6, 22.6, and 20.2. ESIMS: *m/z*: ($M^+ + H$) 366. HRMS calcd for $C_{19}H_{25}NO_4Cl$ (M^++H): 366.1472, found, 366.1476.

Compound **4n**: Pale yellow liquid, IR (KBr): ν_{max} 2925, 2854, 1735, 1641, 1508, 1460, 1378, 1292, 1212, 1124, 1032, 993, 925, 831, 757, 545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, $J = 9.0$ Hz, 2H), 6.77 (d, $J = 9.0$ Hz, 2H), 5.87–5.72 (m, 2H), 5.16 (d, $J = 16.6$ Hz, 2H), 5.07 (d, $J = 11.3$ Hz, 2H), 5.02 (t, $J = 6.0$ Hz, 1H), 4.82 (m, 1H), 4.06 (dd, $J = 6.0$, 12.8 Hz, 1H), 3.95 (dd, $J = 3.0$, 12.8 Hz, 1H), 3.92–3.85 (m, 2H), 3.72 (s, 3H), 3.5 (m, 4H), 2.19 (s, 3H), 2.10 (dt, $J = 3.0$, 12.8 Hz, 1H), 2.01 (s, 3H), 1.80 (ddd, $J = 2.2$, 4.3, 12.8 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 198.0, 158.5, 153.7, 136.5, 134.7, 134.4, 129.4, 117.3, 116.9, 114.5, 108.8, 82.7, 76.1, 72.4, 71.3, 71.2, 69.0, 55.4, 30.5, 30.4, 29.6, 29.3, 28.6, 20.0. ESIMS *m/z*: (M^++H) 414. HRMS calcd for $C_{24}H_{32}NO_5$ (M^++H): 414.2280, found, 414.2277.