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Highly stereoselective cyclopropanation of glycals with cyclic diazoamides: a facile synthesis of spirooxindolyl sugar derivatives

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ABSTRACT

Rhodium(II) acetate catalyzed intermolecular cyclopropanation of glycals with cyclic carbenoids generated from 3-diazo-2-oxindole has been achieved to produce a novel series of spirooxindolyl sugar derivatives in good yields under mild experimental conditions.

The synthesis of 1,2-cyclopropanated sugars and their use in carbon–carbon and carbon–heteroatom bond forming reactions remains an important area of research in sugar chemistry.[1] They are important building blocks in organic synthesis as they undergo ring opening reactions in the presence of NIS,[2a] trimethylsilyltriflate,[2b,2c] $BF_3{\cdot}OEt_2$,[2d] and titanium(IV) chloride[2e] thereby generating C2-branched sugar amino acid derivatives, C2-branched glycosides, seven-membered oxepanes by pyran ring-expansion, and five-membered carbocycles and heterocycles through [3+2] cycloaddition, respectively. The cyclopropanation of glycals provides unique bicyclic structures with high reactivity of cyclopropanes together with extreme optical purity and functional density. The electron donating effect of the oxygen in pyran ring enhances the reactivity of cyclopropane ring for accessing C2-branched glycosides as well as the C1 functionalized carbohydrate scaffolds. Consequently, the cyclopropanation of glycals with diazoacetates has been reported using transition metal catalysts, but the stereoselectivity was controlled by the substituents in sugar moiety. In particular, Baidzhigitova et al. have reported the first example of cyclopropanation of unsaturated sugars with ethyl diazoacetate in the presence of a copper salt with some success in terms of both yield and selectivity.[3]

Later report by Hoberg et al. has made a modest progress in yield, but the progress made is debatable in terms of selectivity. The improvement in selectivity has been achieved by the introduction of sterically more bulky groups such as triisopropylsilyl- and *tert*-butyldimethylsilyl groups at R^3 to block one face of the molecule, thus enabling the cyclopropanation with a good selectivity (Scheme 1).[4]

Following our interest on the use of glycals in sugar chemistry,[5] we were interested to improve the above mentioned protocol by utilizing a modified diazo counterpart.

Surprisingly, no efforts have been made to explore the possible diversity of diazocompounds for the stereocontrolled cyclopropanation of glycals. To modify the diazo compound for stereocontrolled cyclopropanation, 3-diazo-2-oxindole was used as the source of a sterically hindered carbene as it shows good selectivity in cyclopropanation of simple olefins.[6] We assume that an increased bulkiness from the diazo counterpart would play a crucial role in determining the stereoselectivity of the reaction which impelled us to choose the above mentioned diazo compound. Moreover, spirocyclic oxindole motifs are found widely in biologically active natural products.[7] In particular, the spiro[cyclopropan-1,3-oxindoles] are known to exhibit inotropic and herbicidal properties. Furthermore, the ring-expansion of spiro[cyclopropan-1,3-oxindoles] with a range of imines furnishes the spiro[pyrrolidin-3,3′-oxindoles], which constitutes oxindole based natural products.[8] Incorporation of the oxindole moiety onto more bio-relevant sugar skeleton would furnish the spirooxindolyl appended sugar scaffolds. We, herein report a highly stereoselective method for the cyclopropanation of unsaturated sugars with cyclic diazoamides to afford the sugar fused spiro[cyclopropane-1,3′-indolin]-2′-one exclusively as a single isomer.

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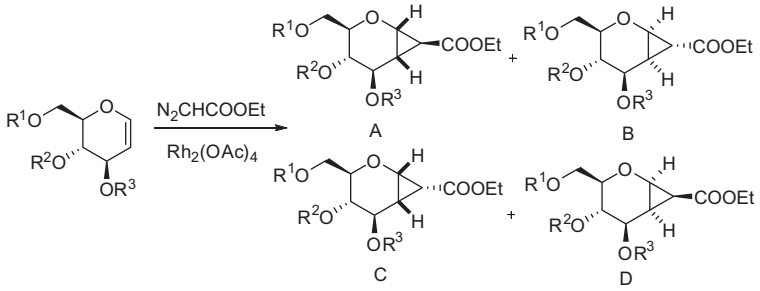
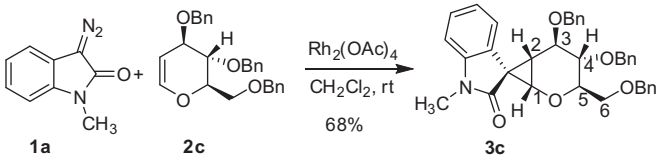


Protecting groups			Product ratio (%)			
R^1	R^2	R^3	A	B	C	D
Ac	Ac	Ac	81	6	4	9
Bn	Bn	Bn	76	8	8	8
TBS	TBS	TBS	97	3	0	0

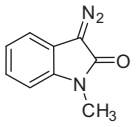
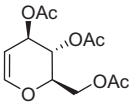
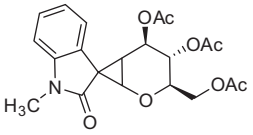
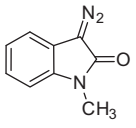
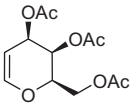
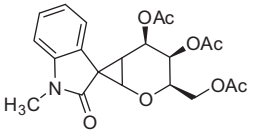
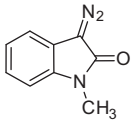
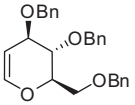
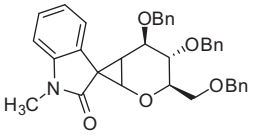
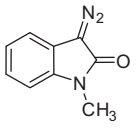
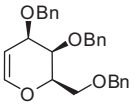
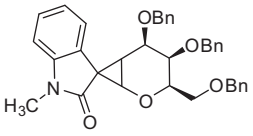
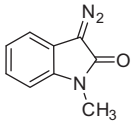
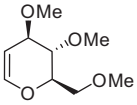
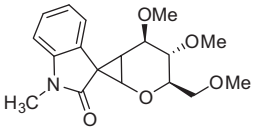
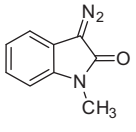
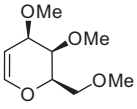
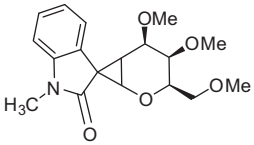
Scheme 1. Reaction of ethyl diazoacetate with D-glucal.



Scheme 2. Cyclopropanation of tri-*O*-benzyl-D-glucal.

Accordingly, we first investigated the coupling of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**1a**) with tri-*O*-benzyl-D-glucal (**2c**) in the presence of 3.0 mol % of rhodium(II) acetate. Interestingly, cyclopropanation of the olefin with diazoamide proceeded smoothly at room temperature and the corresponding

Table 1
Cyclopropanation of glycals with cyclic diazoamides[a]

Entry	Diazo compound (**1**)	Glycal (**2**)	Product[b] (**3**)	Yield[c] (%)
a				64
b				68
c				68
d				74
e				68
f				74

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