Substrate-Controlled Cyclopropanation Reactions of Glycals with Aryl Diazoacetates

Yujing Guo,[a] Chao Pei,[a] and Rene M. Koenigs*[a]

Cyclopropanation reactions of d-glucal and d-galactal derivatives with aryl diazidoacetates can be conducted in a substrate-controlled, stereoselective fashion using simple Rh(II) catalysts, which is further supported by DFT studies. Following this methodology, sugar-derived, donor-acceptor cyclopropanes can be accessed that allow stereoselective O-glycosylation reactions.

Since the advent of metal-catalyzed cycloaddition reactions of carbene intermediates,[1–3] the cyclopropanation reaction of unsaturated oxygen-containing heterocycles has attracted the interest of organic chemists.[4–8] The cyclopropanation reaction of glucal derivatives provides an efficient entry into cyclopropanated sugar molecules and over the past decades this reaction proved highly efficient and versatile using a variety of catalytic or stoichiometric methods.[1–5] Despite these advances current synthesis methods employing carbene transfer reactions are limited to the use of ethyl diazoacetate[8ac] (Scheme 1a), intramolecular processes[4] and cyclic diazoamides.[5] The reaction with donor-acceptor substituted diazoalkanes[6] has, to the best of our knowledge, not been reported yet, although it would constitute an important strategy to introduce molecular complexity and to access cyclopropanated saccharides (Scheme 1b).

Glycosylation reactions constitute an essential strategy for the installment of a diverse array of new functional groups into the 2-position of sugar molecules and are pivotal in modern drug synthesis, polysaccharide synthesis and nucleic acid research.[7–9] The Koenigs-Knorr-type is a classic glycosylation strategy that harnesses a cationic dioxolanium intermediate that can be ring-opened in a highly stereoselective fashion.[8] Following this strategy, cyclopropanated sugars recently emerged as a promising new approach to conduct stereoselective glycosylation reactions while at the same time introducing a carbon side-chain at the 2-position of the sugar molecule for further derivatization.[9] The cyclopropanation product of glucals with donor/acceptor diazoalkanes furnishes a donor-acceptor cyclopropane, which we hypothesized to be amenable to strain-release ring-opening reactions to conduct glycosylation reactions (Scheme 1b).[9–11]

We therefore studied the cyclopropanation reaction of d-glucal with methyl phenyldiazoacetate as a model reaction, yet we could neither observe the formation of the cyclopropane product under photochemical conditions[12] nor in the presence of catalysts based on Cu, Fe or Au (for details, see Table S1 in ESI).[13] Gratifyingly, Rh2(OAc)4 gave a low yield of 10% of the desired product as a single isomer, the stereochemistry of which was assigned by a NOESY experiment (Table 1, entry 2). Further optimization concerned the investigation of different solvents and Rh(II) catalysts, and Rh2(esp)3 was identified as the optimal catalyst, which gave the desired cyclopropane in moderate yield (Table 1, entry 2–4 and Table S1 in ESI).[13] To further increase the product yield, we switched from a one-pot protocol to a slow addition protocol, which was key to obtain the desired cyclopropane in high isolated yield as a single isomer (Table 1, entry 5–7). Intrigued by the exclusive formation of a single diastereoisomer as the reaction product, we next investigated this reaction with chiral Rh(II)-based catalysts. However, no stereoinduction of the Rh(II) catalyst could be
observed and disregarding of the absolute configuration of the Rh(II) catalyst, the same isomer was obtained as in the case of the achiral Rh$_2$(esp)$_2$ catalyst. This underlines that the stereo-selectivity of this cyclopropanation reaction is under substrate rather than catalyst control (Table 1, entry 8–11).

With the optimized conditions in hand, we then set out to study the substrate scope of ester substituted donor-acceptor diazoalkanes in the reaction with α-glucal (Scheme 2a). Different ester functional groups and substituents all positions of the aromatic ring were tolerated and the cyclopropane product could be isolated in high yields, even on gram-scale. The substitution pattern on the aromatic ring had, in the most cases, only little influence; halogen and ether substituents were tolerated in all positions of the aromatic ring, even in the case of an ortho-fluoro substituent a high yield of the cyclopropane product was observed. Only in the case of the benzodioxol- and the electron-poor p-CF$_3$-substituted diazoacetates a reduced yield of the cyclopropane reaction product was obtained. In all cases only a single diastereoisomer of the cyclopropane was observed.

Based on our research interest in fluorinated diazoalkanes$^{[14,15]}$ we next studied fluorinated donor acceptor diazoalkanes 9a–c (Scheme 2b). Under otherwise identical conditions, the desired fluorinated cyclopropanes 10a–c could be isolated in moderate to very good yields, now showing the first examples of cyclopropanation reactions of α-glucal with fluorinated diazoalkanes. Remarkably, we could observe a different stereochemistry in this cyclopropanation reaction of fluorinated diazoalkanes that arises from the opposite facial orientation of one reactant in the transition state of this cyclopropanation reaction (vide infra). In this context, we also studied the reaction of phenyl diazoacetonitrile (11) and trifluoro diazoethane (12), yet only trace amounts of the desired reaction product could be observed for both diazoalkanes by $^1$H-NMR spectroscopy (Scheme 2c).

Next, we embarked on the evaluation of protecting groups of α-glucal (1b–f) in this cyclopropanation reaction (Scheme 3a). Different protecting groups, such as methyl ethers (8p), silyl ethers (8q,r), acetals (8s) and ketals (8t) proved compatible with the present reaction conditions and the desired cyclopropanes could be obtained in moderate to good yields. It is important to note that different protecting groups had no effect on the stereoselectivity of this cyclopropanation reaction. Even a sterically demanding TBS protecting group at the 4’ hydroxy group did not affect the stereoselectivity and only a single isomer was obtained (8q and 8s). We next, studied the reaction of triacetyl-α-galactal (13) under the otherwise identical conditions and the desired cyclopropane 14 was obtained in high isolated yield. Finally, we studied the reaction of the parent cyclopropane 8a in glycosylation reactions with methanol using different Lewis acid catalysts for the strain-release ring opening of the cyclopropane ring. However, only in the case of methanol as both solvent and reactant and using Yb(OTf)$_3$ as catalyst, 8a underwent glycosylation reaction to selectively give the β-anomer 15 of the O-glycosylation product in moderate yield (Scheme 3b).

Intrigued by the high stereoselectivity of this cyclopropanation reaction and the surprising stereochemical differences in the reaction of aryl diazoacetates 7 vs. the trifluoromethylated diazoalkanes 9, we next embarked upon DFT calculations to rationalize the observed selectivity. For this purpose, we first studied the reaction of dihydropyran 16 with methyl phenyl diazoacetate 7a using Rh$_2$(OAc)$_2$ as a simplified model reaction by DFT calculations (Figure 1). This simplified model was used to first identify transition states and reaction pathways of this cyclopropanation reaction. We started our calculations with 7a and Rh$_2$(OAc)$_2$ which undergo formation of a rhodium carbene complex by coordination of the carbon atom of the diazo functional group methyl phenyl diazoacetate with concomitant extrusion of nitrogen gas. The transition state of this metal carbene formation TS$_1$ was calculated with an activation free
energy of 25.6 kcal/mol. This rhodium carbene complex then undergoes cyclopropanation with dihydropyran 16 via side-on attack to the carbene atom (TS2-a or TS2-e), which lead to the formation of two diastereoisomers (17 and 18) of the desired cyclopropane product. In transition state TS2-a, the two planes of the phenyl ring and dihydropyran are in parallel arrangement and thus, there is almost no repulsion between the phenyl ring and dihydropyran. In transition state TS2-e, the ester plane is perpendicular to the dihydropyran plane, which results in steric hindrance and an unfavored transition state. Furthermore two

Scheme 2. Substrate scope with different diazooalkane reaction partners: a) ester-substituted diazooalkanes; b) fluorinated diazooalkanes; c) unreactive diazooalkane reaction partners.

Figure 1. DFT calculations on the simplified cyclopropanation reaction with dihydropyran, level of theory: B3LYP/6-311+G(d,p)(LANL2DZ)(dichloromethane)//B3LYP/6-31G(d) (LANL2DZ).

CiteTable: ChemCatChem 2020, 12, 4014–4018 www.chemcatchem.org
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other transitions states (TS2-c, and TS2-d) were identified, which lead to undesired by-products (See ESI for details). Most importantly, TS2-a possesses the lowest activation free energy of 21.4 kcal/mol and directly leads to the observed isomer of the cyclopropane product.

We next investigated the respective transition states for the cyclopropanation reaction of d-glucal 1a with the intermediate rhodium carbene complex (Table 2) for diazoalkanes 7a and 9a.

First, we studied the reaction of aryldiazoacetate 7a and could identify four different transition states in the reaction with chiral d-glucal leading to all four potential different diastereoisomers of the cyclopropane product. The lowest activation free energy was found for TS1-a, which leads to the formation of the observed diastereoisomer of this cyclopropanation reaction. All other transition states found are significantly higher in energy (> 3.4 kcal/mol, > 300:1 calculation ratio), which accounts for the high diastereoselectivity observed in this transformation. In the cyclopropanation transition state TS1-a, the six-membered ring of d-glucal is parallel to the phenyl group, which reduces the steric repulsion, while the plane of the ester group is perpendicular to d-glucal. In the other transition states, large clashes between the ester group and d-glucal contribute to the unfavorable cyclopropanation transition states. In transition state TS2-a, a slight repulsion between the phenylning and the C–OAc remains, although it has the lowest activation free energy. As a consequence the steric repulsion in both TS1-a and TS1-c result in the decrease of the delta energy compared to dihydropyran (Table 2).

We next focused on the origin of the stereoselectivity in the cyclopropanation of trifluoromethylated diazoalkane 9a. Similarly as for 7a, we could identify four different transition states leading to all potential stereoisomers of 10a. In the transition state TS1-c, the CF3 group shows less space demand than ester group, which reduces the repulsion between the CF3 and C–OAc considerably and consequently leading to a distinctive spatial orientation of the metal-carbene complex and thus addition of d-glucal from the reverse face to the metal carbene complex (Table 2).

| Table 2. Transition states for the cyclopropanation reaction of triacetyl-d-glucal with diazoalkanes 7a and 9a. DFT calculations at the B3LYP/6-311 + G(d,p) (LANL2DZ)/dichloromethane/B3LYP/6-31G(d) (LANL2DZ) level. |
| --- |
| TS name | TS1-a | TS1-b | TS1-c | TS1-d |
| Schematic representation of TS | ![Schematic representation of TS](image) | ![Schematic representation of TS](image) | ![Schematic representation of TS](image) | ![Schematic representation of TS](image) |
| Reaction types | ![Reaction types](image) | ![Reaction types](image) | ![Reaction types](image) | ![Reaction types](image) |
| 7a | ![7a](image) | ![7a](image) | ![7a](image) | ![7a](image) |
| EWG=C02Me | ![7a](image) | ![7a](image) | ![7a](image) | ![7a](image) |
| slight repulsion between the Ph and the C–OAc 0.0 kcal/mol | large repulsion between the CO2Me and the C–OAc 6.2 kcal/mol | repulsion between the CO2Me and the C–OAc 3.4 kcal/mol | repulsion between the Ph and the C–OAc 3.8 kcal/mol |
| 9a | ![9a](image) | ![9a](image) | ![9a](image) | ![9a](image) |
| EWG=CF3 | ![9a](image) | ![9a](image) | ![9a](image) | ![9a](image) |
| repulsion between the Ph and the C–OAc 3.7 kcal/mol | repulsion between the CF3 and the C–OAc 6.3 kcal/mol | slight repulsion between the CF3 and the C–OAc 0.0 kcal/mol | repulsion between the Ph and the C–OAc 6.7 kcal/mol |
In summary, we herein describe the highly diastereoselective cyclopropanation reaction of d-glucal and d-galactal derivatives using a simple Rh(II) catalyst. Under the present reaction conditions, aryl diazoacetates and fluorinated donor acceptor diazolanes react in high efficiency to the desired cyclopropane product in a substrate-controlled fashion (23 examples, up to 92% yield). Initial experiments on glycosylation reactions of these sugar-derived cyclopropanes show a high selectivity for the β-anomer. DFT calculations indicate a distinct difference in activation free energy due to the different steric demand in the cyclopropanation transition states, which renders the whole process highly diastereoselective.

Acknowledgements

Funded by the Boehringer Ingelheim Stiftung via an Exploration Grant. YG and CP gratefully acknowledge the China Scholarship Council for generous support. The authors declare no conflict of interest.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: diazoalkane · carbene · cyclopropanation · sugar

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Manuscript received: April 1, 2020
Revised manuscript received: May 11, 2020
Accepted manuscript online: May 14, 2020
Version of record online: July 7, 2020