Chapter: I  
Part-A  
Gold(III) Chloride Catalyzed Synthesis of Chiral Substituted 3-Formyl Furans from Carbohydrates: Application in the Synthesis of 1,5-Dicarbonyl Derivatives and Furo[3,2-c]pyridine

1. INTRODUCTION

Diversely substituted furans form an important structural motif prevalent in a biologically indispensable natural products, several pharmaceuticals, agrochemicals, as well as flavouring and aroma compounds. They are also useful building blocks found in synthetic organic chemistry, materials chemistry, and self-healing macromolecular materials. Moreover, the functionalized furan core has attracted tremendous attention for designing numerous intermediates and as versatile starting materials for the synthesis of heterocyclic as well as acyclic compounds. Importantly, substituted chiral furans find widespread applications as versatile synthetic intermediates, and are commonly found in many bioactive natural products.

Despite the development of numerous methods for the synthesis of highly substituted furans in the past few years, including transition metal mediated cyclization and cycloisomerization methods, devising efficient access to obtain substituted chiral furans from common precursors remains a challenging task. Among the many methods developed so far, the reaction of metalated furans with the carbonyl group or various other electrophiles, Grignard type addition reaction of furan carbaldehyde with a variety of nucleophiles, and Lewis acid catalyzed Friedel-Crafts type reactions of various carbonyl compounds with furan derivatives are more common. Chiral products may be accessed by the use of chiral pool precursors like carbohydrates, by enzymatic resolution of racemic mixtures, or by kinetic resolution of starting materials. In addition to Garcia Gonzalez reaction, addition/oxidative rearrangement of 3-furfurals with NBS and tandem Suzuki-Miyaura coupling followed by acid catalyzed cyclization also offer new ways to obtain polyhydroxylated furans.

Furthermore, though substituted 3-formyl furan derivatives find widespread applications as synthetic intermediates for the synthesis of bioactive natural products, however, there is a lack of general methods to synthesize them; the few methods available mainly involve the metlation of furan rings followed by formylation. This approach is somewhat restricted, as after metalation addition of electrophiles to furan rings occurs preferentially at the C-2 and C-5 positions, and there is always much difficulty in separation from the unwanted regioisomers. The corresponding chiral products are also potentially important synthetic intermediates; however, their utility is very much underexplored owing to the lack of general methods to synthesize them. As a consequence, establishing more efficient routes to highly substituted chiral 3-formyl furans from easily accessible starting materials continues to captivate the endeavour of synthetic chemists.

A gold(III)-catalyzed efficient access to highly substituted chiral 3-formyl furans under extremely mild conditions using H₂O as a nucleophile from a suitably protected 5-(1-alkynyl)-2,3-dihydro-pyran-4-one has been described. The latter can be prepared from the corresponding appropriately functionalized monosaccharides or commercially available glycals in a few steps following oxidation, iodination, and Sonogashira coupling sequences. To confirm the proposed mechanistic pathway in gold-catalyzed reaction, we employ MeOH as a nucleophile instead of H₂O, and resulting in substituted furo[3,2-c]pyran derivative. The synthesis of a similar skeleton with hybrid carbohydrate-furan derivative is also carried out with PDC oxidation of chiral 3-formyl furan. Furthermore, the substituted 3-formyl furans could then be smoothly subjected to a TiBr₄-catalyzed process to produce 1,5-dicarbonyl compound, which on treatment with NH₄OAc in slightly acidic conditions afforded furo[3,2-c]pyridine.
2. RESULTS AND DISCUSSION

A detailed retrosynthetic strategy towards substituted chiral furans from a suitably substituted 2-iodoglycals as starting material is depicted in Scheme 1. 2-Iodoglycals (2) can easily be synthesized from the corresponding appropriately functionalized monosaccharides, or commercially available glycols, in a few steps by following a well documented literature procedure (see Supporting Information for details).\textsuperscript{18} To obtain the carbohydrate congeners, we used different hexoses such as D-glucose, D-galactose, L-rhamnose, and L-fucose as well as the pentose sugar D-xylose.\textsuperscript{16,19}

**Scheme 1. Retroynthetic analysis and synthetic applications of polyhydroxylated chiral substituted 3-formyl furans from monosaccharides (both hexoses and pentoses) PG = protecting group**

Common protecting groups such as –COCH\textsubscript{3} (acetyl), –CH\textsubscript{2}Ph (benzyl), and -TBDMS (tert-butyldimethylsilyl) were used for hydroxyl group protection in monosaccharides. 2-Alkynylated sugars (3a-p) were synthesized by the Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}/CuI catalyzed standard Sonogashira coupling reaction (Scheme 2).\textsuperscript{16c,20}

We used a variety of different aromatic, aliphatic, and TMS-protected commercially available terminal alkynes as coupling partners. It was found that the alkynes with electron-neutral (3a-e) or electron-donating substituents (3f-j) on the aromatic ring resulted in 2-alkynylated carbohydrates in good to excellent yields (57-90%, Scheme 2). However, the yields were moderate (40-58%, Scheme 2) when substrates with electron-withdrawing substituents (3k-n) on the aromatic ring were employed.

Importantly, trimethylsilyl acetylene was also found to be amenable to the reaction conditions affording the corresponding 2-alkynylated products (3o-p, Scheme 2) in >70% yields. However, the coupling reaction with alkylacetylene did not produce the desired product by following the general procedure (Scheme 2). After several attempts, the coupling reaction with alkylacetylenes was successfully achieved with Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}/Cu/Et\textsubscript{3}N in moderate yields (3q-s, 52-56%, Scheme 2) by following the literature procedure.\textsuperscript{20b,c}
Scheme 2. Synthesis of 5-(1-alkynyl)-2,3-dihydro-pyran-4-ones from substituted 2-iodoglycals by Sonogashira coupling

\[
\text{Pd(PPh}^3\text{)}_2\text{Cl}_2 (5 \text{ mol\%}), \quad \text{Cul (10 mol\%}, \quad \text{DIPEA (3.0 equiv}, \quad \text{THF (dry) (2.0 equiv)} \quad 0 \degree C - \text{r.t.}
\]

\[
\begin{align*}
R^1 &= \text{CH}_2\text{OBn, CH}_2\text{OTBS, Me, H} \\
R^2 &= \text{OBn, OH}
\end{align*}
\]

19 examples yield up to 90%

During our initial investigations, we occasionally found that a solution of 3a in EtOAc showed a marked propensity to undergo cyclization upon exposure to open air resulting in 4a in 50% yield after 48 h. A systematic study of this transformation (to shorten the time period and to achieve higher yields) showed that treating 3a in THF with 0.2 mL of H\textsubscript{2}O as a nucleophile at room temperature furnished 4a in 55%
yield (entry 1, Table 1). Interestingly, treatment with a Brønsted acids such as MeSO$_3$H (methanesulfonic acid), HCl, and HBr failed to improve the yield (32-51%) even after 12-26 h (entries 2-4, Table 1). Other metal catalysts such as CuI, CuBr, AgNO$_3$, PPh$_3$AuCl, and AuCl also catalyzed this transformation, but resulted in moderate to lower yields (entries 5-9, Table 1).

Table 1. Reaction optimization for substituted chiral 3-formyl furans from 3-Benzylxy-2-benzylxymethyl-5-phenylethynyl-2,3-dihydro-pyran-4-one$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol %</th>
<th>Time(min or h)</th>
<th>Yield (%)</th>
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<td>1</td>
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<td>48h</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
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<td>32</td>
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<tr>
<td>3</td>
<td>HCl</td>
<td>10</td>
<td>24h</td>
<td>51</td>
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<tr>
<td>4</td>
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<td>26h</td>
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<tr>
<td>5</td>
<td>CuI</td>
<td>10</td>
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<td>52</td>
</tr>
<tr>
<td>6$^c$</td>
<td>CuBr</td>
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<td>10h</td>
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<tr>
<td>7</td>
<td>AgNO$_3$</td>
<td>10</td>
<td>12h</td>
<td>73</td>
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<tr>
<td>8</td>
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<tr>
<td>9</td>
<td>AuCl</td>
<td>10</td>
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<td>71</td>
</tr>
<tr>
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<td>PPh$_3$AuNTf$_2$</td>
<td>10</td>
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<td>90</td>
</tr>
<tr>
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<td>PPh$_3$AuNTf$_2$</td>
<td>1</td>
<td>20h</td>
<td>89</td>
</tr>
<tr>
<td>12</td>
<td>PPh$_3$AuCl + AgBF$_4$</td>
<td>10</td>
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</tr>
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<td>20$^d$</td>
<td>AuCl$_3$</td>
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<td>10min</td>
<td>42</td>
</tr>
<tr>
<td>21$^e$</td>
<td>AuCl$_3$</td>
<td>10</td>
<td>10min</td>
<td>77</td>
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</table>

$^a$By stirring a mixture of 3a (0.03 g, 0.071 mmol, 1.0 equiv) and catalyst (mol%) in dry THF (2 mL) under Ar atmosphere at room temperature (20-25 °C), employing time as mentioned, followed by quenching with H$_2$O. $^b$Yields are of isolated products. $^c$Reaction was performed at 50 °C. $^d$Reaction was carried out in acetonitrile. $^e$Reaction was carried out in dichloromethane; Tf = trifluoromethane sulfonyl.

However, the more reactive cationic Au(I) catalysts Ph$_3$PAuNTf$_2$ and PPh$_3$AuCl+AgOTf (10 mol%) accelerated the transformations with excellent yields, and the reaction proceeded to completion within 10-15 minutes (entries 10 and 13, 90%, Table 1); whereas 1 mol% of Ph$_3$PAuNTf$_2$ also catalyzed this transformation, but the necessity to conduct the reaction for a longer reaction time (entry 11, 20 h, 89%, Table 1). Inspired by these cationic Au(I) catalyst results, we also explored the scope of this cyclization reaction with Ph$_3$PAuCl+AgBF$_4$. We observed that 10 mol% of this catalyst was not as effective as other gold(I)-catalysts (entry 12, 87%, Table 1). Interestingly, a catalytic amount of AuCl$_3$ (0.5, 0.7, and 1 mol%) were also found to be equally effective (entries 14-16, 90-91% yield, Table 1), but again longer
reaction time were necessary. The use of 5 mol % AuCl₃ accelerated the transformation (entry 17), and the reaction proceeded to completion within 10 minutes (Table 1). The yield was improved further with 10 mol% of AuCl₃ (96% yield, entry 18). AuBr₃ was also found to be almost equally effective (entry 19). The use of other solvents (CH₂CN and DCM) however failed to improve the yield (entries 20 and 21, Table 1). Thus, we concluded that the use of 10 mol% AuCl₃ in THF at room temperature constitutes the optimized reaction condition.

Having established the optimized protocol, we next investigated the substrate scope and generality for this transformation with H₂O as a nucleophile. The Scheme 3 summarizes the results. In general, the reaction is tolerant to variation in substitution/protection at both the alkyne and the 4- and 6-positions of the hexopyranose ring. It is interesting to note that the electronic nature of the aromatic substituents on the alkyne moiety and the substitution/protection in carbohydrate congeners played a significant role in the yield of the reaction. With benzyl as a protecting group for the hexopyranose OH groups, substrates containing electron-neutral (4a-b, 4d-e) or electron-donating (4f-g, 4i-j) substituents on the terminal alkyne resulted in chiral substituted 3-formyl furans in moderate to excellent yields (43-96%, Scheme 3). However, substrates containing electron-withdrawing substituents delivered the corresponding chiral furans (4k-l, 4n) only in moderate yields (42-67%, Scheme 3). Furthermore, replacement of the aryl group with an alkyl group in the terminal alkyne, was also found to be compatible under the reaction conditions, and delivered the corresponding chiral furans (4q-s) in moderate to good yields (52-82%, Scheme 3). When we replaced the benzyl protection for OH groups with a TBDMS group, it lowered the yield dramatically (4c, 4h, 4m; 21-49%, Scheme 3). This may be attributed to the acid hydrolysis of the primary TBDMS group, during the course of the reaction, resulting from the mild acidic property of AuCl₃ in H₂O, as it is well-documented in the literature that a secondary benzylic hydroxyl group protected by TBDMS substitution is stable under gold catalysis. However, the purported products remained to be isolated by silica gel column chromatography. Thus, the possibility of competing intermolecular Reppe-type vinylation resulting from the C-4 hydroxyl group of hexopyranose ring might play an important role for the low yields with TBDMS group.

To achieve higher yields for the entries with <50% yields (Scheme 3), the more reactive cationic gold(I) catalyst was examined. To our pleasant surprise, when we treated 3c with Ph₃PAuNTf₂ (10 mol%)/THF/H₂O at r.t., the corresponding 4c was isolated in 81% yield, and the reaction proceeded to completion within 20 minutes. However, we observed that use of 0.5 mol% Ph₃PAuNTf₂ was not effective to catalyze this transformation (46% yields) even after 44 h. Similarly, under this remarkably mild reaction conditions, the other 2-alknylated glycals (3d and 3h) were converted to their respective furans (4d and 4h) in moderate to good yields compare to the AuCl₃ catalyzed reaction (Scheme 3). Unfortunately, 3k and 3m didn’t produce the corresponding 4k and 4m in satisfactory yields under the same conditions, ostensibly owing to the presence of strong electron withdrawing (-NO₂) group on the aromatic ring (Scheme 3). All the above reactions in Scheme 3 proceeded to full conversion to the product irrespective of the starting materials used, as monitored by TLC. For some of the entries, drop in yield was due to the inherent reactivity of these systems as well as degradation of some of the products during column chromatography (with both silica gel and neutral or basic alumina). Otherwise, most of the substituted chiral furan-aldehydes were stable, and we did not find any difficulty on purification, or storing them for long time. The structures of 3-formyl furan products were assigned by 2D NMR spectroscopy.

The probable mechanism of the reaction may be explained on the basis of that proposed for chromones system. After the initial formation of an activated alkyne–gold intermediate in the presence of AuCl₃, it would undergo either a domino nucleophilic attack by H₂O followed by anti-endo-dig cyclization (Path A, Scheme 4), or the formation of a cyclic oxonium ion with subsequent attack by H₂O (Path B, Scheme 4).
Scheme 3. AuCl₃ and Ph₃PAuNTf₂ catalyzed synthesis of substituted chiral 3-formyl furans from protected 5-(1-alkynyl)-2,3-dihydro-pyran-4-ones

![Scheme 3](image-url)

R¹ = CH₂OBn, CH₂OTBS, Me, H  
R² = OBn, OH  
R³ = aromatic, aliphatic  

<table>
<thead>
<tr>
<th>Compound</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>4a</td>
<td>10</td>
<td>96%</td>
</tr>
<tr>
<td>4b</td>
<td>15</td>
<td>63%</td>
</tr>
<tr>
<td>4c</td>
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<td>49%</td>
</tr>
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<td>4d</td>
<td>20</td>
<td>43%</td>
</tr>
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<td>4e</td>
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</tr>
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<td>4f</td>
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<td>4h</td>
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</tr>
<tr>
<td>4o</td>
<td>15</td>
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¹10 mol% PPh₃AuNTf₂ was used; ²1 mol% PPh₃AuNTf₂ was used; ³5 mol% AuCl₃ was used; ⁴0.5 mol% PPh₃AuNTf₂ was used.
Inspired by the above findings and to further exploit the potential of \(\text{AuCl}_3\) as a catalyst for chiral substituted furan synthesis, the TMS protected 2-alkynylated glycal derivatives (3o and 3p) were treated under the standard reaction conditions. The results are shown in Scheme 5.

To our delight, 3o also underwent \(\text{AuCl}_3\)-catalyzed cyclization and the corresponding furan derivative 4o was obtained only in 9% yield. In addition, products 4oa and 4ob were also isolated in 11% and 16% yields, respectively (Scheme 5). Formation of 4ob could be explained on the basis of removal of the TMS group either prior to or soon after cyclization under slightly acidic reaction conditions (\(\text{AuCl}_3\)-H\(_2\)O), whereas 4oa resulted from a 1,2-Si migration from C-5 to the carbenoid centre generated at C-4.

This unique 1,2-Si migration is particularly attractive as it allows the synthesis of hitherto inaccessible unsymmetrical 2,3-disubstituted C-4 silylated chiral furans. Further work is in progress to increase the yield of the desired product. A perusal of the literature also revealed that the 1,2-Si migration is kinetically favored over 1,2-H migration in case of an Au-carbene intermediate.

Switching to the galacto substrate 3p also revealed the same picture (furan derivative 4p, 35%; and desilylated product 4pb, 30%) except that the 1,2-Si migration product 4pa was isolated only in trace amount (Scheme 5). To achieve higher yields for the unsymmetrical 2,3-disubstituted C-4 silylated chiral furans, the more reactive cationic gold(I) catalysts were examined. To our most disappointment, when we treated 3p with 10 mol% Ph\(_3\)PAuNTf\(_2\) and PPh\(_3\)AuCl+AgOTf respectively, only the corresponding 4pb (30-32%, Scheme 5) was isolated, devoid of any 4p and 4pa. In addition, product 4pc, resulting from the desilylation of 3p before cyclization, was also obtained in 34% and 18% yields, respectively. Subsequently, we successfully performed PPh\(_3\)AuNTf\(_2\)-catalyzed cyclization reaction of 4pc to yield 4pb (48%, Scheme 5).
Scheme 5. Scope for Gold-catalyzed synthesis of polyhydroxylated chiral furans from TMS protected 2-alkynylated glycals

Interestingly, when MeOH was used as a nucleophile instead of H₂O in the AuCl₃-catalyzed cyclization, the corresponding substituted 4-methoxy-2-phenyl-6,7-dihydro-4H-furo[3,2-c]pyran 5a was isolated from 3c in moderate yield (Scheme 6, 55%), which may be considered as a hybrid carbohydrate-furan derivative, and also confirmed the mechanistic pathway described in Scheme 4. The stereochemistry of MeOH addition was assigned on the basis of NOESY experiment. Furthermore, synthesis of substituted furo[3,2-c]pyran-4-one (5b) could be possible upon PDC oxidation of chiral substituted furan 4a (Scheme 6, 40%).


To demonstrate the potential utility of the highly substituted polyhydroxylated furan derivatives, we undertook a synthesis of 2-phenyl substituted furo[3,2-c]pyridine. Substituted furo[3,2-c]-pyridines form a key structural unit in drugs and biologically active natural products, and exhibit a wide range of pharmaceutical activities. Due to their potential applications, a number of synthetically useful routes...
have been developed for their synthesis.\textsuperscript{28} Furthermore, literature survey revealed that treatment of α,β-unsaturated 1,5-dicarbonyl derivatives with NH\textsubscript{4}OAc under mild acidic conditions delivered the corresponding substituted pyridine in good to excellent yield.\textsuperscript{29}

We therefore became interested in the synthesis of the key intermediate α,β-unsaturated 1,5-dicarbonyl derivatives from our synthesized furan products. When we treated 4a or 4b with TiBr\textsubscript{4} (2 equiv) in toluene under refluxing conditions, the corresponding 1,5-dicarbonyl derivative 6 was isolated in 43\% yield (Scheme 7).

**Scheme 7. Synthesis of substituted 2-phenyl-furo[3,2-c]pyridine via 1,5-dicarbonyl derivative**

The mechanism of the reaction may be explained on the basis of generation of the oxonium cationic species (II), through TiBr\textsubscript{4} mediated formation of complex (I) with secondary –OBn group, as described in Scheme 7.\textsuperscript{30} Rearomatization of the furanoid ring and subsequent tautomerization afforded α,β-unsaturated 1,5-dicarbonyl derivative 6. With the α,β-unsaturated 1,5-dicarbonyl precursor in hand, we next turned our attention to the synthesis of substituted furo[3,2-c]pyridine following the literature procedure.\textsuperscript{29} The treatment of 6 with EtOH/NH\textsubscript{4}OAc under mild acidic conditions at 40 °C indeed delivered the corresponding 2-phenyl substituted furo[3,2-c]pyridine 7 in 60\% yield (Scheme 7).

**3. CONCLUSION**

In conclusion, we have successfully developed an efficient general route to densely functionalized chiral 3-formyl furans from suitably protected 5-(1-alkynyl)-2,3-dihydro-pyran-4-ones using catalytic AuCl\textsubscript{3} and water as a nucleophile. The reactions proceeded under mild conditions and resulted in moderate to excellent yields. The protected 5-(1-alkynyl)-2,3-dihydro-pyran-4-ones have been prepared from the corresponding monosaccharides following oxidation, iodination, and Sonogashira coupling sequences. The potential of this approach has been described by the preparation of a substituted furo[3,2-c]pyridine derivative following two steps reaction sequences; a TiBr\textsubscript{4}-catalyzed reaction of the 3-formyl furan derivatives has resulted 1,5-dicarbonyl compound, which on treatment with NH\textsubscript{4}OAc in slightly acidic conditions afforded substituted furo[3,2-c]pyridine. The scope and limitations of these new densely functionalized chiral furans towards synthesis of biologically active heterocycles are currently under study in our laboratory.
4. EXPERIMENTAL SECTION

4.1 General Information:

Melting points were determined in open-end capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f<sub>254</sub>), and the spots were visualized with UV light (254 and 365 nm) or by charring the plate dipped in 5% H<sub>2</sub>SO<sub>4</sub>-MeOH or 5% H<sub>2</sub>SO<sub>4</sub>/vanillin/EtOH solution. <sup>1</sup>H (300 MHz and 600 MHz) and <sup>13</sup>C NMR (75 MHz and 150 MHz) spectra were recorded in CDCl<sub>3</sub> solvent using TMS as the internal standard. HRMS (m/z) were measured using EI and ESI techniques. Infrared (IR) spectra were recorded on Fourier transform infrared spectroscopy, only intense peaks were reported. Optical rotations were recorded at 589 nm.

4.2 General Procedure for the Synthesis of 3a-p:

To a flame-dried two-necked round bottom flask, equipped with a magnetic stir bar and rubber septa, corresponding iodo compounds (2a-g, 1.0 equiv) in dry THF (10mL/mmol) were taken separately. PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 equiv), terminal alkyne (2.0 equiv), and CuI (0.1 equiv) were added into flask at 0 °C and then DIPEA (3.0 equiv) was added drop-wise to the resulting mixtures and allowed to stir at room temperature for required times. After completion of reaction (TLC), saturated NH<sub>4</sub>Cl solution was added and the product was extracted with EtOAc. The combined organic layers were dried over anhyd Na<sub>2</sub>SO<sub>4</sub> and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The crude residue was purified over silica gel column chromatography [230-400; eluent: ethyl acetate/hexane] to obtain 3a-p. These compounds should not be either stored in solution or exposed to open air for a long time, as they showed a marked propensity to undergo cyclization resulting in mixtures of 3a-p and 4a-p. Due to this tendency for cyclization, HRMS for some of these derivatives were not matched exactly.

4.3 General Procedure for the Synthesis of 3q-s:

To a flame-dried two-necked round bottom flask, equipped with a magnetic stir bar and rubber septa, corresponding iodo compounds (2a-b, 1.0 equiv) and the respective aliphatic terminal alkyne (2.0 equiv) were dissolved in NEt<sub>3</sub> (30 mL/mmol) separately. PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol %) and CuI (10 mol %) were subsequently added into flask, and the resulting mixtures were allowed to stir at room temperature for required times. After completion of reaction (TLC), saturated NH<sub>4</sub>Cl solution was added and the product was extracted with EtOAc. The combined organic layers were dried over anhyd Na<sub>2</sub>SO<sub>4</sub> and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The crude residue was purified over silica gel column chromatography [230-400; eluent: ethyl acetate/hexane] to obtain 3q-s.

4.4 Characterization Data of 3a:

3-Benzyloxy-2-benzzyloxymethyl-5-phenylethylnyl-2,3-dihydro-pyran-4-one (3a): 2a (0.1 g, 0.222 mmol) was converted to 3a (0.08 g, 85%) following the general procedure A; eluent, EtOAc/n-hexane (8%); [α]<sub>D</sub><sup>20</sup> = +147 (c = 0.1 in MeOH); yellow gum; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.74 (s, 1 H), 7.47 - 7.50 (m, 2 H), 7.30 - 7.38 (m, 13 H), 5.08 (d, J = 11.1 Hz, 1 H), 4.62 (d, J = 10.8 Hz, 1 H), 4.51 - 4.64 (m, 3 H), 4.29 (d, J = 10.8 Hz, 1 H), 3.82 ppm (d, J = 3.0 Hz, 2 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 190.3, 165.3, 137.3, 137.1, 131.6 (2 x CH), 128.5 (4 x CH), 128.4 (2 x CH), 128.2 (3 x CH), 128.1, 127.9, 127.8 (2 x CH), 122.9, 103.7, 92.3, 81.6, 79.3, 74.5 (CH<sub>2</sub>), 73.7, 73.6 (CH<sub>2</sub>), 67.7 ppm (CH<sub>2</sub>); IR (KBr): v<sub>max</sub> 2217, 1694, 1604, 1588, 1247, 1149, 1102 cm<sup>-1</sup>; HRMS (ESI, m/z) calcd for C<sub>28</sub>H<sub>24</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup>: 447.1573; found: 447.1943.
4.5 General Procedure for the Synthesis of 4a-s:

In a 25 mL flame-dried two-necked round bottom flask, equipped with a magnetic stir bar, the corresponding substituted ethynyl-2,3-dihydro-pyran-4-one (3a-s) was dissolved in dry THF (2.5 mL) at room temperature under argon atmosphere. AuCl₃ (mol%) or PPh₃AuNTf₂ (mol%) or PPh₃Au+AgOTf (mol%) was added to the reaction mixtures and was stirred for required times. The resulting reaction mixtures were quenched with H₂O, saturated NH₄Cl solution was added, and the product was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The crude residue was purified over silica gel column chromatography [230-400; eluent: ethyl acetate/hexane] to afford 4a-s.

4.6 Characterization Data of 4a:

2-(1,3-Bis-benzyloxy-2-hydroxy-propyl)-5-phenyl-furan-3-carbaldehyde (4a): 3a (0.05 g, 0.117 mmol) was converted to 4a (0.05 g, 96%) following the general procedure: eluent, EtOAc/hexane (25%); [α]D²⁰ = +59 (c = 0.1 in MeOH); yellow gum; ¹H NMR (600 MHz, CDCl₃): δ = 10.01 (s, 1 H), 7.68 - 7.69 (m, 2 H), 7.40 - 7.43 (m, 2 H), 7.29 - 7.36 (m, 2 H), 7.23 - 7.24 (m, 2 H), 6.99 (s, 1 H), 4.93 (d, J = 7.8 Hz, 1 H), 4.61 (d, J = 11.4 Hz, 1 H), 4.56 (d, J = 12.0 Hz, 1 H), 4.52 (d, J = 11.4 Hz, 1 H), 4.43 (d, J = 12.0 Hz, 1 H), 4.31 (dt, J = 4.2, 7.2 Hz, 1 H), 3.74 (dd, J = 4.8, 9.6 Hz, 1 H), 3.70 (dd, J = 3.6, 9.0 Hz, 1 H), 2.57 ppm (br. s., 1 H); ¹³C NMR (150 MHz, CDCl₃): δ = 185.2 (d, 1 C), 159.5, 154.9, 137.6, 136.8, 129.3, 128.8 (2 x CH), 128.5 (2 x CH), 128.5, 128.5 (2 x CH), 128.3, 128.2, 128.1 (2 x CH), 127.9, 127.8 (2 x CH), 124.3 (2 x CH), 102.6, 73.8, 73.6 (CH₂), 71.8 (CH₂), 71.7, 70.2 ppm (CH₂); IR (KBr): v max 1678 cm⁻¹; HRMS (EI, m/z) calcd for C₂₈H₂₆O₃ [M⁺]: 442.1780; found: 442.1777.

4.7 Synthesis and Characterization Data of 7:

6-Benzylxymethyl-2-phenyl-furo[3,2-c]pyridine (7): 1,5-dicarbonyl derivative 6 (0.022 g, 0.066 mmol) was dissolved in a solution of NH₄OAc (50.7 mg, 0.66 mmol, 10 equiv) and acetic acid (0.04 mL, 0.66 mmol, 10 equiv) in ethanol (0.01 M with respect to 6). The resulting mixture was heated at 40 °C for 12 h. After completion of reaction (TLC), the reaction mixture was cooled to room temperature and diluted with ethyl acetate, washed with aqueous saturated NaHCO₃ solution, and followed by brine solution. The combined organic layers were dried over anhyd Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to get a crude residue. The crude residue was purified over silica gel column chromatography to obtain 7 (0.012 g, 60%); eluent: EtOAc/hexane (35%); light yellow solid; mp = 88 °C; ¹H NMR (600 MHz, CDCl₃): δ = 8.84 (s, 1 H), 7.86 - 7.87 (m, 2 H), 7.68 (s, 1 H), 7.47 (t, J = 7.2 Hz, 2 H), 7.36 - 7.43 (m, 5 H), 7.30 - 7.32 (m, 1 H), 7.05 (s, 1 H), 4.83 (s, 2 H), 4.70 ppm (s, 2 H); ¹³C NMR (150 MHz, CDCl₃): δ = 160.3, 157.1, 153.9, 142.7, 138.0, 129.5, 129.3, 128.9 (2 x CH), 128.4 (2 x CH), 127.8 (2 x CH), 127.7, 125.5, 125.2 (2 x CH), 104.6, 99.0, 73.0 (CH₂), 72.9 ppm (CH₂); HRMS (ESI, m/z) calcd for C₂₃H₁₈NO₃ [M + H⁺]: 316.1337; found: 316.1104.

5. REFERENCES


6. NMR SPECTRA
$^1$H (300 MHz), $^{13}$C (75 MHz) NMR spectra of 3a
$^{1}H$ (600 MHz), $^{13}C$ (150 MHz) NMR spectra of 4a
$^1$H (600 MHz), $^{13}$C (150 MHz) NMR spectra of 7
Part-B

Chiral Substituted 3-Formylfurans from Carbohydrates: An Expedient Route via N-
Bromosuccinimide (NBS)-Mediated Electrophilic Cyclization

1. INTRODUCTION

Chiral, substituted furans in general and diversely substituted, chiral 3-formylfurans in particular are commonly found in many bioactive natural products, and are also important syn-thons in synthesizing highly complex target structures (Figure 1). However, only a few synthetic methods exist for the efficient syntheses of chiral, substituted 3-formylfurans, thereby precluding their utility for further transformations. Like its chiral version, there are only sporadic reports on efficient synthetic strategies for racemic substituted 3-formylfurans. The classical methods mainly involve either reduction of carboxylic acids/esters or metalation of furan rings at the C3 position followed by formylation, which is generally applicable if the C2 and C5 positions of furan are occupied to avoid the formation of unwanted regioisomers. Recently, transition-metal-catalyzed 3-formylfuran syntheses from acyclic precursors have also been reported as an alternative to the existing approach-es. It is worth mentioning that one of the great remaining challenges in furan chemistry is selective introduction of a formyl group at the C3 position.

Recently, we have disclosed a gold(III)-chloride-catalyzed effi-cient route to substituted chiral 3-formylfurans from suitably protected 5-(1-alkynyl)-2,3-dihydropyran-4-ones derived from carbohydrate scaffolds, utilizing H2O as a nucleophile. How-ever, this method requires highly expensive and air-sensitive gold catalysts, which limit its broad applicability. On the other hand, electrophilic heteroatom cyclization of functionally sub-stituted alkenes has emerged as a powerful tool in organic synthesis for the generation of wide variety of heterocycles. Because of their ready availability and high functional group tolerance, electrophilic reagents are frequently employed in disparate reactions.

Accordingly, taking into consideration the halonium-induced electrophilic cyclization and carbohydrates as stereoselective tools, we proposed a retrosynthetic analysis of diversely substi-tuted chiral 3-formylfurans from easily accessible starting materials (Scheme 1). We speculated that if the olefinic p-bond of 2 could form a halonium ion intermediate A, an oxonium ion B would be generated. Subsequently, intramolecular nucleophilic attack by oxygen would then proceed smoothly, followed by the addition of H2O to generate chiral, substituted 3-formylfurans 3 (Scheme 1).

2. RESULTS AND DISCUSSION

To validate this idea (Scheme 1), substituted 2-iodoenones I were synthesized from the appropriately functionalized, readily available, and inexpensive monosaccharides or com-mercially available glycals (D-glucose, D-galactose, L-fucose, L-rhamnose, and D-xylose) in a few steps according to the known literature procedures.

The 2-alkenylated sugars were prepared by Pd-catalyzed Heck coupling of 1 with activated or unactivated terminal olefins. After preliminary screening with different Pd catalysts, ligands, bases, and solvents (Table 1), the optimized conditions were found to be Pd(OAc)2/PPh3/Ag2CO3/DMF (entry 7, Table 1).

The results of the Heck coupling under optimized conditions are summarized in Scheme 2 and Scheme 3. The reactions of styrenes containing electron-neutral (2a-d), electron-donating (2e-j), electron-deficient (2k-m), or strongly electron-with-drawing (2n) substituents on the aromatic ring, or that with a naphthyl...
Scheme 1. General Strategy Towards the Synthesis of Chiral Substituted 3-Formylfurans from Carbohydrates

Table 1. Optimization Studies for Heck-Coupling

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst(mol %)</th>
<th>ligand(mol %)</th>
<th>base(equiv.)</th>
<th>solvent</th>
<th>t(h)</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>K$_2$CO$_3$(2)</td>
<td>DMF</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Et$_3$N(3)</td>
<td>DMF</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Et$_3$N(3)</td>
<td>DMF</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Ag$_2$CO$_3$(2)</td>
<td>DMF</td>
<td>7</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Ag$_2$CO$_3$(2)</td>
<td>DMA</td>
<td>5.5</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Ag$_2$CO$_3$(2)</td>
<td>CH$_3$CN</td>
<td>6</td>
<td>55</td>
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<tr>
<td>7</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Ag$_2$CO$_3$(3)</td>
<td>DMF</td>
<td>5.5</td>
<td>80</td>
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<tr>
<td>8</td>
<td>Pd(OAc)$_2$(10)</td>
<td>Xanthphos(20)</td>
<td>Ag$_2$CO$_3$(3)</td>
<td>DMF</td>
<td>7</td>
<td>55</td>
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<tr>
<td>9</td>
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<td>XPhos(20)</td>
<td>Ag$_2$CO$_3$(3)</td>
<td>DMF</td>
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<td>67</td>
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<td>PPh$_3$(20)</td>
<td>Ag$_2$CO$_3$(3)</td>
<td>DMF</td>
<td>5</td>
<td>73</td>
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<tr>
<td>11</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Ag$_2$CO$_3$(3)</td>
<td>DMA</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$(10)</td>
<td>PPh$_3$(20)</td>
<td>Ag$_2$CO$_3$(3)</td>
<td>DCE</td>
<td>5</td>
<td>65</td>
</tr>
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</table>

By stirring a mixture of 1b (0.05 g, 1.0 equiv), styrene (2.0 equiv), catalyst (mol%), ligand (mol%), base (equiv) in 4.0 mL solvent under an Ar atmosphere at room temperature (30-40 °C) for the designated time period; Yields are of isolated E-olefin; almost negligible amount of Z-olefins were formed in few cases.

substituent (2o) delivered the corresponding Heck-coupled products in moderate to good yields (Scheme 2). Interestingly, despite the presence of halides (chloro, bromo, and fluoro) in the styrenes, no evidence of halide substitution was detected in the product (2k–m, Scheme 2). tert-Butyl acrylate was also found to be compatible with the reaction conditions (2p, Scheme 2).

However, the reactions of unactivated olefins bearing allylic protons gave an inseparable mixture of isomeric olefins (2q–s, Scheme 3), including minor amounts of expected olefins (2qa, 2ra, and 2sa). This is ascribed to the varying degree of β-hydride elimination and regioisomeric carbopalladation (migratory insertion), as described in the literature. 7b,d,s Gratifyingly, the reactions with N-allylphthalimide and a
Scheme 2. Substrate scope for activated olefins

The reactions were carried out with 1 (0.1 g, 1.0 equiv.), olefins (2.0 equiv.), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), and Ag$_2$CO$_3$ (3.0 equiv.) at RT. Yields are of isolated E-olefins; almost negligible amount of Z-olefins were formed in few cases. For 2p the reaction was performed at 60 °C.

substituted allyl phenyl ether worked decently well, and only the E isomer was selectively obtained (2t and 2u, Scheme 3). The trans alkene stereochemistry in the products 2 was confirmed by the large coupling constant between the olefinic protons ($^3$J = 15.6–16.8 Hz) in the $^1$H NMR spectra.

Next, to optimize the reaction conditions for chiral, substituted 3-formylfurans, we initiated a systematic study with 2h as a substrate. As shown in Table 2, electrophilic reagents such as NCS, NIS, I$_2$, NBP, Br$_2$, and PPh$_3$·HBr/DMSO$^9$ could all catalyze this transformation, but the product 3h was formed in lower yields/trace amounts (entries 2–5 and 9–10, Table 2). Interestingly, the use of 1.2 equivalents of NBS in THF furnished 3h in 66 % yield (entry 6); employing NBS in higher (1.0 equiv.) or higher (1.5 equiv.) ratios only reduced the yields (entries 7–8). Further, incorporation of different additives, such as p-toluene sulfonic acid monohydrate (TsOH·H$_2$O), acetic acid, benzoic acid, silver salts, or Et$_3$N, along with NBS also failed to improve the yields (entries 11–17, Table 2). The additives did not have any substantial effect on this cyclization. Among the solvents tested (entries 18–20, Table 2), THF was found to be the most effective. Thus, we concluded that the combination of NBS (1.2 equiv.)/H$_2$O/THF constitutes the optimum reaction conditions.
Scheme 3. Substrate scope for unactivated olefins

Reactions were carried out with 1 (0.1 g) under the reaction conditions in Scheme 2, and isolated yield is shown. 2qa–qc, 2ra–rc, and 2sa–sc were inseparable mixtures.

Having established the protocol for the optimum conditions, the substrate scope was examined. The results are shown in Scheme 4. It is noteworthy that the electronic nature of the aromatic substitution/protection at both the olefins and the carbohydrate components did not influence the outcome of reactions significantly, except when strongly electron-withdrawing groups were present in the olefins. In general, the reactions of Heck-coupled products with activated styrenes containing electron-neutral (2a–d), electron-donating (2e–i), or electron-deficient (2k–m) substituents on the aromatic ring, or that with a naphthyl substituent (2o) gave 2,5-disubstituted-3-formylfurans with polyhydroxylated side chains in moderate to good yields. An advantage of this transformation is the transfer of chirality from the carbohydrate to product 3 without employing any expensive chiral catalyst or ligand (Scheme 4).

Moreover, D-xylose-derived Heck product 2j also underwent NBS-mediated cyclization and the chiral furan derivative was isolated in 30 % yield (3j, Scheme 4). In this case, product 3ja was also isolated in 11 % yield as an inseparable mixture of α and β anomers in a 6:1 ratio, resulting from the conjugate addition of 3j to 2j via cyclic bromonium ion formation (see Scheme 7 below). The major diastereomer was assigned as the α anomer by comparison of NMR data with known furo[3,2-c]pyran derivatives. To determine the compatibility of a nitro-substituted aromatic group with the reaction conditions, 2n was examined. This reaction produced only trace amount of the required product (3n, Scheme 4), perhaps owing to the lack of sufficient electron density on the olefin. Further examination of substrates revealed that an acrylate ester was also not suitable for this transformation (Scheme 4); in this case, a substituted 2,3-dihydrofuran derivative (3pa) was isolated along with other unidentified products (see Scheme 7 below for mechanistic details). We then investigated the scope of Heck products 2t and 2u containing unactivated olefins as substrates for NBS-mediated cyclization. Unfortunately, all attempts toward cyclization led to only formation of inseparable mixtures of several compounds, and the desired products 3t and 3u were isolated only in trace amounts, ostensibly owing to the lack of aromatic conjugation.
Table 2. Optimization Studies for Chiral 3-Formylfurans

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent(equiv.)</th>
<th>solvent</th>
<th>additive(equiv.)</th>
<th>t</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>THF</td>
<td>-</td>
<td>48h</td>
<td>n.d^b</td>
</tr>
<tr>
<td>2</td>
<td>NCS (1.2)</td>
<td>THF</td>
<td>-</td>
<td>15h</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>NIS (1.2)</td>
<td>THF</td>
<td>-</td>
<td>36h</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>I2 (1.2)</td>
<td>THF</td>
<td>-</td>
<td>24h</td>
<td>8^c</td>
</tr>
<tr>
<td>5</td>
<td>NBP (1.2)</td>
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<td>30min</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
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<td>-</td>
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<td>61</td>
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<td>-</td>
<td>20min</td>
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<tr>
<td>9</td>
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<td>CH2Cl2</td>
<td>-</td>
<td>2h</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>PPh3.HBr (2.0)</td>
<td>DMSO</td>
<td>-</td>
<td>7h</td>
<td>30^d</td>
</tr>
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<td>THF</td>
<td>TsOH.H2O (1.2)</td>
<td>45min</td>
<td>58</td>
</tr>
<tr>
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<td>THF</td>
<td>TsOH.H2O (0.1)</td>
<td>15h</td>
<td>35</td>
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<tr>
<td>13</td>
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<td>THF</td>
<td>CH2COOH (1.2)</td>
<td>1h</td>
<td>51</td>
</tr>
<tr>
<td>14</td>
<td>NBS (1.2)</td>
<td>THF</td>
<td>PhCOOH (1.2)</td>
<td>45min</td>
<td>58</td>
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<tr>
<td>15</td>
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<td>THF</td>
<td>AgOTf (0.1)</td>
<td>1h</td>
<td>54</td>
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<tr>
<td>16</td>
<td>NBS (1.2)</td>
<td>THF</td>
<td>AgSBF4 (1.2)</td>
<td>1h</td>
<td>48</td>
</tr>
<tr>
<td>17</td>
<td>NBS (1.2)</td>
<td>THF</td>
<td>Et3N (1.2)</td>
<td>24h</td>
<td>n.d^b</td>
</tr>
<tr>
<td>18</td>
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<td>CH2CN</td>
<td>-</td>
<td>30min</td>
<td>54</td>
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<tr>
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<td>NBS (1.2)</td>
<td>1,4-Dioxane</td>
<td>-</td>
<td>30min</td>
<td>45</td>
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<tr>
<td>20</td>
<td>NBS (1.2)</td>
<td>DMF</td>
<td>-</td>
<td>30min</td>
<td>48</td>
</tr>
</tbody>
</table>

*2h (0.03 g, 0.068 mmol, 1 equiv.) in solvent (1.5 mL mmol^-1) at 0 °C for 20–30 min under an Ar atmosphere, followed by addition of H2O (30 equiv.). The reaction mixtures were stirred at RT (if required) for the remaining time period. Yields are of isolated products. ^bNot detected, starting materials isolated. ^cMixture of several spots. ^dHeated to 50 °C. NBS = N-bromosuccinimide; NCS = N-chlorosuccinimide; NIS = N-iodosuccinimide; NBP = N-bromophthalimide; Tf = trifluoromethanesulfonyl.

Next, the preparation of the more challenging fully substituted chiral 3-formylfuran was studied with our two-step approach from 1b. Thus, 1b was reacted with β-methylstyrene (cis and trans mixture) under the conditions detailed in Scheme 2 but at 50 °C. This indeed afforded Heck-coupled products (cis- and trans-mixture) which could be subjected to NBS-H2O-mediated cyclization to afford the fully substituted chiral 3-formylfuran 3v in 30% overall yield in two steps (Scheme 5). It must be mentioned here, the synthesis of fully substituted chiral 3-formylfuran by using this NBS-THF-H2O method provided a direct and strategic advantage over Au(III)-catalyst as it might be relatively difficult to achieve by gold-catalyzed reaction.

We thought that the modest yields achieved in this electrophilic cyclization (Scheme 4 and Scheme 5) might be due to the Achmatowicz reaction, as it is widely recognized that the substituted furans undergo addition/oxidative rearrangement with NBS to form substituted pyranones. However, no such oxidized products were isolated. Meanwhile, the structures of all compounds in Scheme 4 were assigned by 2D NMR spectroscopy and comparison of NMR data with known derivatives.

[^2h]: 0.03 g, 0.068 mmol, 1 equiv.) in solvent (1.5 mL mmol^-1) at 0 °C for 20–30 min under an Ar atmosphere, followed by addition of H2O (30 equiv.). The reaction mixtures were stirred at RT (if required) for the remaining time period. Yields are of isolated products.

[^b]: Not detected, starting materials isolated.

[^c]: Mixture of several spots.

[^d]: Heated to 50 °C. NBS = N-bromosuccinimide; NCS = N-chlorosuccinimide; NIS = N-iodosuccinimide; NBP = N-bromophthalimide; Tf = trifluoromethanesulfonyl.
Scheme 4. Synthesis of chirally substituted 3-formylfurans\(^a\)

\[
\begin{align*}
\text{R}^1 & \quad \text{O} \quad \text{R}^2 & \quad \text{O} \quad \text{R}^3 \\
\text{2} & \quad + \quad \text{H}_2\text{O} & \quad \text{NBS (1.2 equiv)} & \quad \text{THF (2.0 mL), 0 \text{o C - r.t.,}} & \quad 10 \text{ min - 16 h} \\
& \quad \quad \quad & \quad \quad \quad & \quad \quad \quad & \quad \quad \quad \quad \quad \text{yield up to 78\%}
\end{align*}
\]

\[3a; 1 \text{ h, 78\%} \]
\[3b; 45 \text{ min, 60\%}\(^b\) \]
\[3c; 40 \text{ min, 53\%} \]
\[3d; 1 \text{ h, 52\%} \]
\[3e; 1 \text{ h, 64\%} \]
\[3f; 10 \text{ min, 55\%}\(^b\) \]
\[3g; 45 \text{ min, 52\%} \]
\[3h; 30 \text{ min, 66\%}\(^b\) \]
\[3i; 10 \text{ min, 55\%}\(^b\) \]
\[3j; 25 \text{ min, 30\%}\(^b\) \]
\[3k; 2 \text{ h, 60\%} \]
\[3l; 1 \text{ h, 52\%} \]
\[3m; 40 \text{ min, 51\%} \]
\[3n; \text{trace}\(^c\) \]
\[3o; 30 \text{ min, 61\%}\(^b\) \]
\[3p; \text{not detected} \]
\[3pa; 16 \text{ h, 28\%}\(^d\) \]

\(^a\)By stirring a mixture of 2 (0.05 g, 1.0 equiv), THF (2.0 mL), NBS (1.2 equiv/mmol) at 0 \text{o C (10-30 min), followed}

by addition of H\(_2\)O (30.0 equiv/mmol). The reaction mixtures were stirred at rt (30-40 °C) for the remaining time

period (if required); Yields are of isolated products. \(^b\)The reaction was performed at 0 °C. \(^c\)Mixture of several spots.

\(^d\)Other unidentified spots were isolated.

Scheme 5. Synthesis of tetrasubstituted chiral 3-formylfuran

\[
\begin{align*}
\text{BnO} & \quad \text{O} & \quad \text{BnO} & \quad \text{I} \\
\text{1b (0.1 g; 0.22 mmol)} & \quad (2-Iodogalactal) & \quad \text{Heck Coupling} & \quad \text{NBS-H}_2\text{O} & \quad \text{THF, 0 °C, 0.5 h} & \quad \text{3v; 30\%} & \quad (\text{overall yield in two-steps}) \\
& \quad & \quad & (\text{Scheme 2}) & \quad (\text{Scheme 4}) & \quad & \\
& \quad & \quad & \text{7 h, 50 °C} & \quad & \quad & \\
& \quad & \quad & \text{(Scheme 2 conditions)} & \quad & \quad & \\
& \quad & \quad & \text{(Scheme 4 conditions)} & \quad & \quad & \\
\end{align*}
\]
On the basis of the above results, we propose a plausible mechanism for the NBS/H$_2$O-mediated electrophilic cyclization, as depicted in Scheme 6. The reaction pathway begins with initial formation of the cyclic bromonium ion intermediate I from the olefinic double bond, followed by immediate formation of cyclic oxonium ion II through intramolecular nucleophilic attack by the oxygen atom. Subsequently, intermediate II can undergo addition of H$_2$O at the anomeric center to furnish III, which, through elimination of HBr, yields 3 (pathway A, Scheme 6). Alternatively, intermediate I could also undergo a domino nucleophilic attack by H$_2$O followed by cyclization and subsequent HBr elimination to produce 3 (pathway B, Scheme 6).

**Scheme 6. Proposed mechanism for chirally substituted 3-formylfurans 3**

The formation of 3pa could be explained on the basis of a cyclic bromonium ion intermediate IV, which undergoes ring opening with H$_2$O followed by concomitant elimination of HBr to produce epoxide VI, and subsequent formation of 3pa via an oxonium ion intermediate (Scheme 7).

**Scheme 7. Proposed reaction mechanism for the formation of 3ja and 3pa**

To expand the domain of our method, we extended the Heck coupling and NBS-mediated cyclization sequence to include MeOH as a nucleophile instead of H$_2$O for the generation of diastereomeric furo[3,2-c]pyran derivatives (4, a/b=6:1, Scheme 8). The configuration at the anomeric center for the major diastereomer, a pseudoaxial glycoside, was assigned on the basis of a 1D NOESY experiment. Additionally, fully protected chiral furan was synthesized from 3h by following a two-step protocol of NaBH$_4$-mediated reduction of the aldehyde to an alcohol and treatment of the resulting di-alcohol with NaH/BnBr to obtain the desired furan 5 (Scheme 9).
3. CONCLUSION

In conclusion, we have successfully developed a general route to obtain chiral, substituted 3-formylfurans from easily accessible substituted 2-iodoenones derived from glycals, through a Heck coupling and NBS/H$_2$O-mediated cyclization sequence. Synthetic manipulations with the same sequence of reactions provide the corresponding fully substituted chiral 3-formylfuran, a furo[3,2-c]pyran derivative, and a fully protected chiral furan. In particular, the use of naturally occurring, inexpensive, and readily available carbohydrates as a source of predefined chirality enable the synthesis of only the desired isomer, circumventing the possibility of any unwanted regioisomer formation. Research is currently in progress to further utilize 2-iodoglycals as potentially important synthetic precursors in target and diversity oriented synthesis.

4. EXPERIMENTAL SECTION

4.1 General Information:

Melting points were determined in open-end capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f$_{254}$), and the spots were visualized with UV light (254 and 365 nm) or by charring the plate dipped in 5% H$_2$SO$_4$/MeOH or vanillin charring solution. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ or [D$_6$]DMSO solvent using tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra were measured in using EI (magnetic sector, positive ion) and ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded on a Bruker Tensor 27 Fourier-transform infrared spectrometer, only intense peaks are reported.

4.2 General Procedure for the Synthesis of 2:

Ag$_2$CO$_3$ (3.0 equiv., vacuum dried) was placed in a 25 mL twoneck, round-bottom flask under an Ar atmosphere. The corresponding starting materials 1 in DMF (4.0 mLmmol$^{-1}$) were added. PPh$_3$ (20 mol%), olefin (2.0 equiv), and Pd(OAc)$_2$ (10 mol%) were introduced separately into the reaction mixtures at room temperature, and the mixtures were stirred at the same temperature or heated with stirring for the time mentioned. After completion of the reaction (determined by TLC), saturated ammonium chloride solution was added, and the product was extracted with EtOAc. The combined organic layers were dried
over anhydrous Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The crude residue was purified by silica gel column chromatography (230–400; eluent: ethyl acetate/n-hexane) to obtain 2. The Heck-coupled products 2 should not be stored for a long time, as they showed a marked tendency to undergo extensive degradation into several unidentified spots. The analytical data for all compounds were collected immediately upon purification.

4.3 Characterization Data of 2a:

\((2R,3R)-3-(Benzyloxy)-2-((benzyloxy)methyl)-5-((E)-styryl)-2,3-dihydro-4H-pyran-4-one\)  

(2a): Prepared according to the general procedure discussed above: eluent: EtOAc/n-hexane (7:93); isolated yield=0.060 g, 63%; \([\alpha]_D^{20} = +210\) (c=0.055 in MeOH); light yellow gum. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta=7.56\) (s, 1 H), 7.42 (d, \(J=7.5\) Hz, 2 H), 7.29-7.33 (m, 12 H), 7.20-7.24 (m, 2 H), 6.62 (d, \(J=16.2\) Hz, 1 H), 5.10 (d, \(J=11.1\) Hz, 1 H), 4.61-4.65 (m, 1 H), 4.57 (d, \(J=6.6\) Hz, 2 H), 4.45-4.52 (m, 1 H), 4.29 (d, \(J=11.4\) Hz, 1 H), 3.82 ppm (d, \(J=3.3\) Hz, 2 H); \(^13\)C NMR (75 MHz, CDCl₃): \(\delta=192.4, 160.4, 137.7, 137.5, 137.4, 128.9, 128.6\) (2 CH), 128.5 (2 CH), 128.5 (2 CH), 128.4 (2 CH), 128.0, 127.9, 127.8 (2 CH), 127.4, 126.2 (2 CH), 119.0, 114.9, 80.8, 74.6 (CH₂), 74.1, 73.6 (CH₂), 67.9 ppm (CH₂); IR (KBr): \(\tilde{\nu}_{max}=1682, 1589, 1452, 1397, 1105, 1071, 745, 698\) cm\(^{-1}\); HRMS (ESI): m/z calcd for C₂₆H₂₆O₅Na [M+Na]⁺: 449.1729; found: 449.1731.

4.4 General Procedure for the Synthesis of 3:

To a stirred solution of 2 (0.05 g, 1.0 equiv.) in anhydrous THF (2.0 mL) was added NBS (1.2 equiv.) at 0 °C under an Ar atmosphere and the resulting solution was stirred for 10–30 min under that temperature. H₂O (30 equiv.) was added. The resulting mixture was stirred at room temperature for the required time (if needed). After completion of the reaction (determined by TLC), saturated ammonium chloride solution was added, and the product was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The crude residue was purified by silica gel column chromatography (230–400; eluent: ethyl acetate/n-hexane) to obtain 3.

4.5 Characterization Data of 3a:

\(2-((1R,2R)-1,3-Bis(benzyloxy)-2-hydroxypropyl)-5-phenylfuran-3-carbaldehyde\)  

(3a):\(^{3a}\) Prepared according to the general procedure discussed above: eluent: EtOAc/n-hexane (22:78); isolated yield=0.040 g, 78%; yellow gum. \(^1\)H NMR (600 MHz, CDCl₃): \(\delta=10.00\) (s, 1 H), 7.68 (dd, \(J=1.2, 8.4\) Hz, 2 H), 7.41 (d, \(J=7.2\) Hz, 2 H), 7.29-7.36 (m, 9 H), 7.23-7.24 (m, 2 H), 6.99 (s, 1 H), 4.93 (d, \(J=7.2\) Hz, 1 H), 4.61 (d, \(J=11.4\) Hz, 1 H), 4.56 (d, \(J=12.0\) Hz, 1 H), 4.52 (d, \(J=12.0\) Hz, 1 H), 4.43 (d, \(J=12.0\) Hz, 1 H), 4.29-4.32 (m, 1 H), 3.74 (dd, \(J=4.8, 9.6\) Hz, 1 H), 3.69 (dd, \(J=4.2, 9.6\) Hz, 1 H), 2.59 ppm (br. s., 1 H); \(^13\)C NMR (150 MHz, CDCl₃): \(\delta=186.3, 160.5, 155.9, 138.5, 138.6, 130.3, 129.8\) (2 CH), 129.6 (2 CH), 129.5, 129.5 (2 CH), 129.4, 129.2, 129.1 (2 CH), 128.9, 128.9 (2 CH), 125.3 (2 CH), 103.6, 74.8, 74.6 (CH₂), 72.9 (CH₂), 72.7, 71.2 ppm (CH₂); HRMS (ESI): m/z calcd for C₂₅H₂₅O₃Na [M+Na]⁺: 465.1678; found: 465.1674. Analytical data are consistent with previously reported values.

5. REFERENCES:


6. NMR SPECTRA
$^1$H (300 MHz), $^{13}$C (75 MHz) NMR spectra of 2a
$^1$H (600 MHz), $^{13}$C (150 MHz) NMR spectra of 3a