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Facile Access to Novel [60]Fullerenyl Diethers and [60]Fullerene–Sugar Conjugates via Annulation of Diol Moieties

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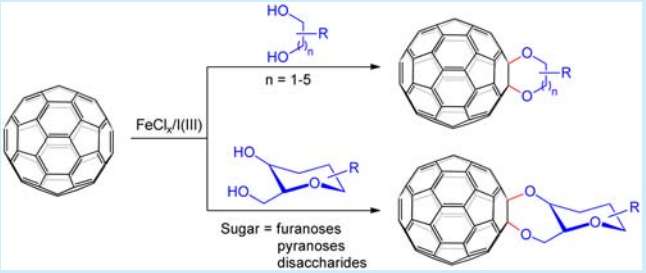
Supporting Information

ABSTRACT: A general and facile annulation of various diol motifs to [60]fullerene has been developed. This protocol can afford not only 6- to 10-membered-ring fullerenyl diethers in one step from simple acyclic diols but also directly couple [60]fullerene with a variety of structurally diverse sugars. The [60]fullerene-sugar conjugates formed do not require any linker moiety and maintain their inherent structural integrity. The electrochemistry of the fullerenyl diethers and [60]-fullerene-sugar conjugates has also been investigated.



Fullerenes functionalized with bioactive molecules are particularly valuable in material science and biological chemistry.[1] Among the numerous bioactive [60]fullerene (C_{60}) derivatives, C_{60}-sugar conjugates have attracted significant attention due to their intrinsic biological properties.[2]

Until now, the most straightforward method was the conjugation of C_{60} with functionalized sugars,[2,3] of which the anomeric C–O bonds were cleaved and further transformed into other functional groups. The glycosylidene carbene addition of glycosylidene-derived diazirines,[3a] the cycloaddition of per-*O*-acetyl glycosyl azides,[3b] and the Prato reaction involving sugar aldehydes[3c] have been utilized to synthesize fullerene glycoconjugates. An alternative strategy is based on the postfunctionalization of C_{60} derivatives, including aziridino [2′,3′:1,2][60]fullerene (C_{60}NH), [60]fullerenoacetyl chloride, [60]fullerene cyclohexanol, alkynes, and so forth.[4] However, these approaches required a suitable linker on the C_{60} surface to couple with sugars in the final step. Apparently, these sugars were not directly anchored to C_{60} but rather were attached through a linker. Furthermore, the synthesis of such linker-functionalized C_{60} derivatives suffered from tedious multistep processes. Thus, facile and direct access to C_{60}-sugar conjugates not requiring any linker moiety and maintaining the structural integrity of sugars is demanding and challenging.

The structural forms of sugars are diverse. Nevertheless, the most common structural units are pyranose and furanose moieties, both of which have rich diol motifs. Although diol motifs are ubiquitous in various sugars, the diol motif as a functional handle to conjugate sugars with C_{60} has not been reported, and even the reaction of diols themselves with C_{60} is scarcely reported.[5] Iron salts[6] and hypervalent iodine(III) reagents[7] have been utilized to promote various reactions of fullerenes. We recently reported the synthesis of oxazolidino-fullerenes by the $FeCl_3$-catalyzed reaction of C_{60} with *tert*-butyl N-substituted carbamates in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA).[6i] Herein, we report a combined system of $FeCl_x$ and hypervalent iodine(III) reagents for the annulation of a series of structurally diverse diols to C_{60}, which provides general and facile access to 6- to 10-membered-ring fullerenyl diethers, and more importantly, enables the unprecedented direct functionalization of C_{60} with various mono- and disaccharides utilizing diol motifs.

At the onset, the simplest ethylene glycol (**1a**) was chosen as a model substrate to optimize the reaction conditions. Gratifyingly, in the presence of $FeCl_2$ and *m*-chloroperoxybenzoic acid (*m*CPBA), the reaction provided the desired product **2a**, albeit in low yield (5%) (Table 1, entry 1). Further investigation revealed that the hypervalent iodine(III) reagent showed efficiency that was superior to other oxidants. Using phenyliodine(III) diacetate (PIDA) gave **2a** in 11% yield (Table 1, entry 2). Furthermore, replacing PIDA with PIFA, the yield was improved to 21% (Table 1, entry 3). Other oxidants such as di-*tert*-butyl peroxide (DTBP) and $K_2S_2O_8$ were totally inactive in the reaction (Table 1, entries 4 and 5, respectively). Control experiments were subsequently conducted. In the absence of either Fe(II) or oxidant, no reactions occurred (Table 1, entries 6 and 7, respectively). Moreover, other iron salts were also explored together with PIFA. Using ferric perchlorate gave the product in 11% yield (Table 1, entry 8), whereas $FeCl_3$ delivered only 6% yield with complete consumption of C_{60} (Table 1, entry 9). Disappointingly, the

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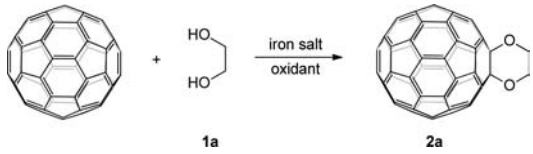
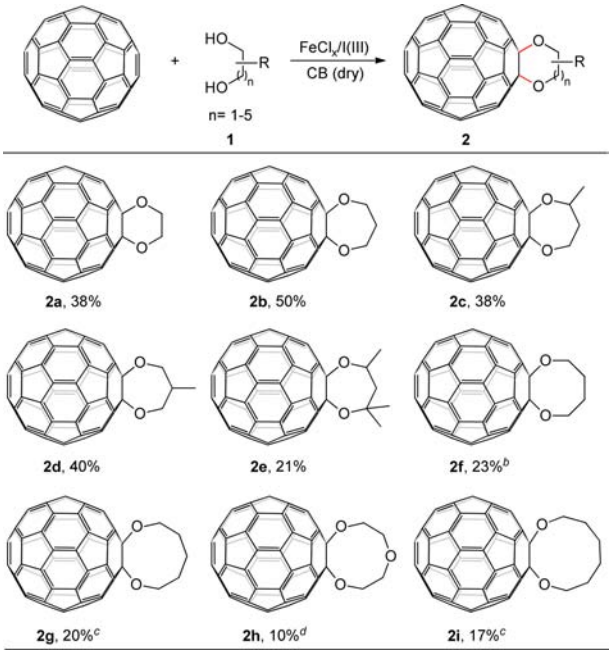
Table 1. Optimization of the Reaction Conditions for the Reaction of C_{60} with 1a[a]



entry	Fe salt	oxidant	yield (%)[b]
1	$FeCl_2$	*m*CPBA	5 (21)
2	$FeCl_2$	PIDA	11 (39)
3	$FeCl_2$	PIFA	21 (32)
4	$FeCl_2$	DTBP	NR
5	$FeCl_2$	$K_2S_2O_8$	NR
6	$FeCl_2$		NR
7		PIFA	NR
8	$Fe(ClO_4)_3{\cdot}xH_2O$	PIFA	11 (51)
9	$FeCl_3$	PIFA	6 (6)
10	$FeCl_3$		NR
11	$FeSO_4{\cdot}7H_2O$	PIFA	trace
12[c]	$FeCl_2$	PIDA/PIFA	38 (86)
13[c]	$FeCl_3$	PIDA/PIFA	27 (38)
14[c,d]	$FeCl_2$	PIDA/PIFA	17 (77)
15[c,e]	$FeCl_2$	PIDA/PIFA	31 (58)
16[c,f]	$FeCl_2$	PIDA/PIFA	25 (63)
17[c,g]	$FeCl_2$	PIDA/PIFA	24 (41)

[a]Unless otherwise specified, all reactions were conducted with a 1:5:3:3 molar ratio of C_{60}/**1a**/Fe salt/oxidant at 100 °C for 1 h. [b]Isolated yield; numbers in parentheses are based on consumed C_{60}. [c]C_{60}/**1a**/Fe salt/PIDA/PIFA at 1:5:3:1.5:1.5. [d]For 0.5 h. [e]For 1.5 h. [f]At 80 °C. [g]At 120 °C.

Scheme 1. Reaction Conditions and Yields for the Reaction of C_{60} with Diols 1a–i[a]



[a]Unless otherwise indicated, all reactions were conducted with a 1:5:3:1.5:1.5 molar ratio of C_{60}/**1**/$FeCl_2$/PIDA/PIFA at 100 °C for 1 h. [b]C_{60}/**1f**/$FeCl_2$/PIDA at 1:5:3:3. [c]Ten equiv of substrates was used. [d]C_{60}/**1h**/$FeCl_3$/PIDA/PIFA at 1:2:3:1.5:1.5 at 130 °C for 2.5 h.

desired product could not be obtained using $FeCl_3$ alone (Table 1, entry 10). Nevertheless, a trace amount of the product was observed when $FeSO_4{\cdot}7H_2O$ was used (Table 1, entry 11). Interestingly, when PIDA and PIFA were utilized simultaneously together with $FeCl_2$, the product yield was improved to 38% (Table 1, entry 12). However, when $FeCl_3$ was used with PIDA/PIFA, the reaction afforded the desired product in a decreased yield (27%) (Table 1, entry 13 relative to entry 12). Variation of the reaction time (Table 1, entries 14 and 15) or temperature (Table 1, entries 16 and 17) did not improve the product yield.

With the optimal conditions in hand, we then examined the substrate scope. As shown in Scheme 1, the C_{60}-fused dioxepanes **2b–d** were efficiently obtained from different 1,3-diols in 38–50% yields. Although the C_{60}-fused dioxane/dioxepane derivatives **2a–c** have been accessed through transetherization of fullerenyl boronic esters in the presence of PTSA at 150 °C, it suffered from a two-step manipulation, harsh reaction conditions, and poor substrate scope.[6f] Hence, the present one-pot procedure is more efficient and straightforward. Because of steric hindrance, highly substituted 1,3-propanediol **1e** delivered an inferior result, giving only 21% yield. Encouraged by the successful construction of 6- and 7-membered-ring fullerenyl diethers, we expanded our methodology to synthesize more challenging fullerene derivatives with 8-membered and larger rings, which could not be achieved under previous protocols. To our delight, the C_{60}-fused 1,4-dioxocane **2f** was obtained in 23% yield when 3 equiv of PIDA was used. The more challenging C_{60}-fused 1,4-dioxonane **2g** was generated in 20% yield by increasing the amount of **1g** to 10 equiv. To our great pleasure, diethylene glycol **1h** was also compatible with the established procedure, and it furnished the C_{60}-fused 9-crown-3 **2h**, in which the [6,6]-bond of C_{60} was incorporated into the crown ether, albeit in 10% yield.[8] Excitingly, the reaction also proceeded well with 1,6-hexanediol **1i**, which led to the desired 10-membered-ring cycloadduct **2i** in 17% yield by increasing the amount of **1i** to 10 equiv. It is known that the majority of C_{60} cycloadducts are limited to 3- to 6-membered rings except for a few examples involving C_{60}-fused 7-membered-ring formations;[9] however, the construction of larger rings in one step have not been reported to date. Predictably, the medium-sized heterocycles, particularly the C_{60}-fused 9-crown-3, may have potential applications in the selective detection of metal ions.[10]

To highlight the synthetic utility of this method, we applied a wide range of structurally diverse sugars containing a residual diol moiety to the established protocol (Scheme 2). To our delight, when α-D-glucofuranoses **1j** and **1k** were employed, the reactions proceeded well and afforded the 6-membered-ring C_{60}-sugar conjugates **2j** and **2k** through C6–OH and C5–OH in 25% and 23% yields, respectively. Interestingly, this transformation was also compatible with various pyranoses, and the 7-membered-ring C_{60}-sugar conjugates were successfully obtained through C6–OH and C4–OH. The tri-*O*-methyl and tri-*O*-acetyl protected α-D-glucopyranoses **1l** and **1m** provided the corresponding products **2l** and **2m** in 28% and 17% yields, respectively. 1-*O*-Methyl-2,3-*O*-isopropylidene-protected α-D-mannose **1n** could be employed, giving the expected product **2n** in 26% yield. Gratifyingly, disaccharides could also react smoothly, and the hexa-*O*-acetyl lactose **1o** gave the desired product **2o** in 15% yield. In comparison with the previous work, this glycosylation protocol features a novel and unique conjugation mode that the linkage is not at the anomeric center, and it does not require any linker moiety, but

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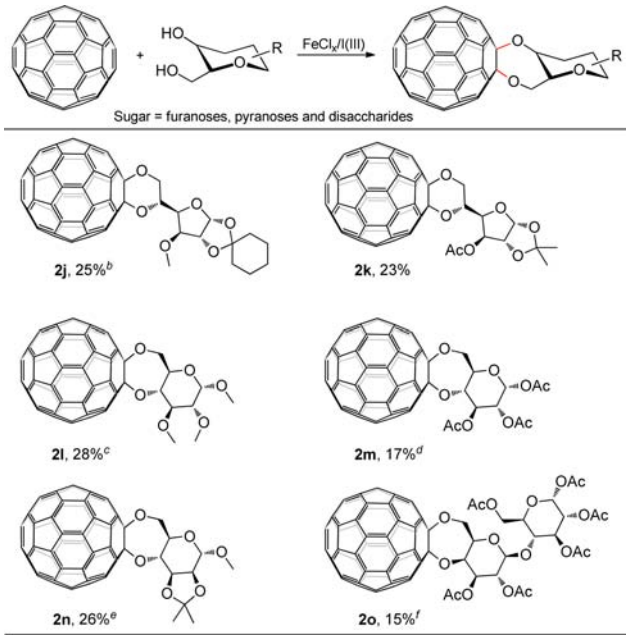
Scheme 2. Reaction Conditions and Yields for the Reaction of C_{60} with Sugars 1j−o[a]

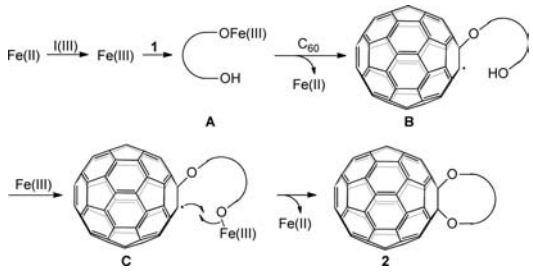


[a]Unless otherwise indicated, all reactions were conducted with a 1:5:3:1.5:1.5 molar ratio of C_{60}/**1**/$FeCl_2$/PIDA/PIFA at 80 °C for 1.5 h. [b]C_{60}/**1j**/$FeCl_3$/PIDA at 1:3:2:2 at 100 °C for 2 h. [c]At 100 °C for 2 h. [d]C_{60}/**1m**/$FeCl_3$/PIDA at 1:5:2:2 at 80 °C for 3 h. [e]At 120 °C for 1.5 h. [f]C_{60}/**1o**/$FeCl_2$/PIDA at 1:5:3:3 at 100 °C for 2 h.

rather directly couples with C_{60} in one step through two C−O σ covalent bonds, where the diol moiety is just like two stretching hands directly catching the C_{60} surface. Therefore, the distance between the sugar moiety and C_{60} is the shortest. Furthermore, our protocol retains the structural integrity of sugars, and the remaining anomeric C−O bonds allow the C_{60}-functionalized sugars for further transformations.

On the basis of the reaction results described above, a reaction mechanism is proposed, as shown in Scheme 3. Under

Scheme 3. Proposed Reaction Mechanism



the screening conditions, we found that the hypervalent iodine(III) reagent in combination with both Fe(II) and Fe(III) salts could trigger the reaction. Therefore, we speculate that an Fe(III) species is initially formed in situ in the presence of hypervalent iodine(III) reagents when Fe(II) is used and then coordinates with a diol to generate complex **A**. Addition of complex **A** to C_{60} generates the fullerenyl radical **B** accompanied by the elimination of another Fe(II) species. Subsequently, the remaining hydroxyl group coordinates with another molecule of the Fe(III) species to form complex **C**. Finally, intramolecular cyclization with the loss of an Fe(II) species affords the corresponding product **2**. For the present annulation reaction of diols, the combination of Fe(II) and I(III) was more effective in most cases, whereas the admixture of Fe(III) and I(III) was more efficient in a few cases. It is possible that the in situ generated Fe(III) species is more reactive than a commercial Fe(III) reagent. However, the exact reason for this phenomenon is not immediately clear.

The half-wave reduction potentials of compounds **2a−o** along with C_{60} are summarized in Table S1 in the SI. All the fullerenyl diethers and C_{60}-sugar conjugates had similar cyclic voltammogram (CV) behaviors and showed three redox processes under our conditions. Owing to the two attached heteroatoms,[6e,11] the first reduction potentials of fullerenyl diethers **2a−i** were generally negatively shifted by only 22−59 mV relative to that of C_{60}. With the increase of the ring size from 6 to 10, the electronegativity of fullerenyl diethers **2a−g** and **2i** was gradually reduced. This is reasonable because the alkyl chain is a donating group, and the donating property is increased with elongation of the chain length. Interestingly, the alternation of the protecting group of 3-*O*-methyl to the corresponding 3-*O*-acetyl obviously changed the reduction potentials, and the first reduction potentials of **2k** and **2m** shifted positively by 24 and 35 mV relative to those of **2j** and **2l**, respectively, and were nearly identical to that of C_{60}. Similarly, the CV behavior of disaccharide derivative **2o** protected by six electron-withdrawing acetyl groups resembled those of **2k** and **2m**, and its first reduction potential was equal to that of C_{60}. These CV behaviors may be attributed to the through-space orbital interactions of the acetyl group.[12] CV investigations of **2a−o** hinted that they should have similar reactivity as C_{60} and thus facilitate further functionalization on the fullerene skeleton of these fullerenyl diethers and C_{60}-sugar conjugates.

In conclusion, we have developed a highly attractive and general protocol for the direct annulation of diverse diol scaffolds to C_{60} in a combined system of iron salt and hypervalent iodine(III) reagent. The current method can not only selectively provide 6- to 10-membered-ring fullerenyl diethers by controlling the distance between the two hydroxyl groups of the diols but also display the synthetic utility to construct novel C_{60}-sugar conjugates from mono- and disaccharides. This intriguing glycosylation methodology requires no linker moiety and maintains the inherent structural integrity. Therefore, the present protocol provides a new avenue to functionalize C_{60} with various biomaterials containing a suitable diol motif.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data, NMR spectra, CVs, and differential pulse voltammograms of **2a−o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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