Regioselective addition of Grignard reagents to tosylazafuleroid and derivatization to 1,2-disubstituted [60]fullerene†

Naohiko Ikuma,* Koji Nakagawa, Ken Kokubo and Takumi Oshima

Grignard reagents (RMgBr: R = Et, p-tolyl) selectively attacked the β-position of the bridgehead double bond of tosylazafuleroid through interaction of Mg with the S=O group. The following [5,6] ring closure and C−N bond scission led to aryl/alkyl aminylfullerenes with 1,2-configuration. Tolyl-substituted aminylfullerene was further converted into 1,4-di(p-tolyl)fullerene on treatment in acidic toluene.

Introduction

Multiple functionalization of fullerene C601–8 is an important process for the materials application of fullerenes, because the introduced substituents modify their electronic properties and enhance their solubility to make them suitable for wet-processing. For example, introduction of multiple substituents improves the open-circuit voltage (Voc) of a fullerene photo-voltaic cell due to the elevation of its LUMO level.2,3 However, regiocontrolled sequential multi-functionalization is still a challenging topic because fullerene C60 has the equivalent of 30 double bonds; the second addition to the monoadduct often leads to various regioisomeric diadducts with a statistic ratio.1 To overcome this difficulty, facile regioselective multi-addition has eagerly been explored using copper reagents,4,5 halogenations,6 some radical reactions,7 and tether-directed procedures.1c,8 Nevertheless, it would also be desired to improve the regioselectivity of the second addition to the monoadducts so that the selective combination of two reactants allows a wide variety of introduced substituents with different roles. In fact, difunctionalized fullerenes with aryl and alkyl groups brought about a change in both electronic properties and solubility.4 Moreover, an unprecedented reaction can be found for the monoadduct as its reactivity is rather different from the pristine C60 caused by the first introduced substituents. In order to attain highly regioselective multiaddition, [5,6] open azafulleroid,9 has been employed as such a synthetic intermediate with ambident reactivity at the bridged nitrogen and the adjacency of the initially obtained 1,2-substituted aminylfullerene.

Results and discussion

Grignard reaction to azafulleroid 1

As seen in Table 1, Grignard reaction of RMgBr (R = Et, p-tolyl) with azafulleroid 1 gave C2-symmetric monoadducts 2a,b via introduction of the R group atug the β-carbon and the ring closure of the [5,6] open bridge associated with C−N bond scission. At room temperature, the alkyl Grignard reagent gave multiadducts or regioisomeric monoadducts as byproducts, while at low temperature 2a was isolated in moderate yield in spite of lower conversion (Fig. S1†). On the other hand, the...
aryl Grignard reagent has high regioselectivity at room temperature. Nevertheless, excess amounts of Grignard reagents gave inseparable multiadducts because the fullerene sphere can undergo further Grignard additions. The regioselectivity could be ascribed to the steric hindrance and Mg-coordination with the tosyl group (Ts) as well as its electron-withdrawing effects. In the expected intermediary, the negative charge appearing on C_α would accelerate the following ring-closure and C–N scission. The appearance of the TsNH group was confirmed by deuteration with D_2O (Fig. S2, in ESI†).

Theoretical study on regioselective addition

To reveal the regioselectivity of azafulleroid 1, we have relied on the DFT energy calculations for the possible geometric transition states. To simplify calculations, only C_α/C_β additions of 1 with PhMgBr (in place of p-tolylMgBr) and EtMgBr were considered and clustering of the Grignard reagent in the initial state was ignored. Due to the S–N bond rotation and the Mg coordination of the TsN group, four possible TS structures were examined for the C_α and C_β additions, respectively. As seen in Fig. 1(a) and (b), regioselectivity for C_β-addition can be explained by the DFT calculations (Tables S1–S4†).

The smallest ΔE‡ value was attained in TS(2-C_β) both for PhMgBr (16.0 kJ mol⁻¹, Fig. 1(c)) and EtMgBr (25.6 kJ mol⁻¹, Table S4†). The noticeable difference of activation energy (18 kJ mol⁻¹ vs. 3-Ca) between C_α/C_β would explain the high regioselectivity for aryl Grignard reagents, while the small difference (8 kJ mol⁻¹ vs. 1-Ca) for the less hindered ethyl reagent may result in the reduced C_β-selectivity. As compared to the reaction of C_60 (ΔE‡ = +75.8 kJ mol⁻¹ for PhMgBr, Fig. 1(d)), the higher reactivity of 1 can be rationalized by the lower LUMO (Fig. 2) and release of strain energy of the anti-Bredt double bond. The C_β-selectivity is mainly attributed to the steric effect of both the tosyl group and Grignard substituents as well as the O⋯Mg coordination effect, rather than the electronic effect because neither charge values (both Mulliken and NBO, Fig. S3†) nor LUMO distribution are remarkable on C_β in comparison with C_α.

Table 1 Addition of alkyl/aryl Grignard reagents to tosylazafulleroid 1

<table>
<thead>
<tr>
<th>RMgBr</th>
<th>Temp./°C</th>
<th>Time/min</th>
<th>Yield of 2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = Et^\text{t} (3 equiv.)</td>
<td>25^\circ C</td>
<td>5</td>
<td>16 (2a)</td>
</tr>
<tr>
<td>p-Tolyl^\text{t} (3 equiv.)</td>
<td>25^\circ C</td>
<td>10</td>
<td>91 (2b)</td>
</tr>
<tr>
<td>(5 equiv.)</td>
<td>25^\circ C</td>
<td>10</td>
<td>51 (2b)</td>
</tr>
</tbody>
</table>

a 3 M Et_2O solution. b 1 M THF solution. c o-Dichlorobenzene (o-DCB) solvent. d CH_2Cl_2 solvent.
Theoretical study on ring-opening

From the product analysis, the generated Cβ-addition intermediate would undergo [5,6] ring-closure and cleavage of one C–N bond (see scheme in Table 1). Since the bond reorganization is essential for obtaining relatively-limited 1,2-di-substituted fullerenes, TS calculations for this process for the PhMgBr adduct were carried out with DFT (Fig. 3 and 4). The addition of PhMgBr through the TS(2-Cβ) configuration resulted in the formation of INT1 with interaction of Mg and the anionic Cα-center. Ring-closure and C–N bond scission seem to be almost concerted processes due to the negligible energy difference between INT2 and TS(α2 scission), although INT2 is a stationary point without an imaginary frequency. The slightly larger energy barrier of ring-closure is partly ascribed to the destabilization of Mg–Cα1 dissociation. If the Ts group rotates, Cβ⋯Mg coordination becomes possible with high energetic stabilization during 5,6-closure and α2 scission processes as shown in Fig. S4.† The C–N cleaved INT3 obtains very large energy of stabilization due to the coordination of the anionic nitrogen on Mg’Br as well as the cleavage of the strained aziridine ring (Fig. 4). Finally, INT3 leads to 1,2-diadduct 2 on acidic quenching.

**Further substitution via 1,2-aminylfullerene**

We attempted acid catalyzed substitution of 1-aryl-2-aminylfullerene to induce further functionalization by replacing the tosylamino group. Similar to the reaction of 1-aryl-4-aminylfullerene,† treatment of 2b in o-DCB with trifluoromethanesulfonic acid (TFOH) and toluene (5 equiv.) provided 1,4-ditolylfullerene 3 via elimination of tosylamide (Scheme 1). This compound has 1,4-configuration with C1 symmetry, indicating that steric hindrance of the tolyl group inhibits the formation of the 1,2-diadduct.

**Conclusions**

Regioselective addition of Grignard reagents was performed on the β-carbon of the bridgehead double bond of tosyl substi-
tuted azafulleroid 1. The high regioselectivity was attained by the steric and coordination effect of the tosyl group. The Mg-coordinated intermediate was degraded into 1-alkyl/2-aminyl fullerene via [5,6] ring-closure and C–N bond scission. The 1,2-adducts are expected to undergo further derivatization owing to the presence of the tosylamino group. The reaction mechanism was supported by the DFT calculations. These results will provide significant information regarding regioselective heterodifunctionalization of fullerenes with the relatively rare 1,2-configuration.

Experimental

Synthesis of azafulleroid 1

Tosyl azafulleroid 1 was prepared by the previously reported method.9e

Grignard reaction of tosyl azafulleroid 1

Grignard reagent (3 M ethyl magnesium bromide in Et2O or 1 M tolylmagnesium bromide in THF) was added to a solution (FAB-MS) of azafulleroid 1 in vacuo chromatography (CS2/CHCl3 eluent) to give product of azafulleroid 1 M tolylmagnesium bromide in THF) was added to a solution of azafulleroid 1 (20 mg) in dichloromethane (10 mL) at ~70 °C (for 2a) or in anhydrous o-DCB at room temperature (2b), respectively, and stirred for 5–15 min. The reaction solution was washed with saturated aqueous NH4Cl solution and fractionated. The organic layer was dried over MgSO4 and evaporated in vacuo. The residue was purified by silica gel column chromatography (CS2/CHCl3 eluent) to give product 2a, b as a dark brown solid.

2a: 1H-NMR (270 MHz, CDCl3 : C S2 = 1 : 1): δ 1.92 (t, 3H, J = 7.3 Hz), 2.33 (s, 3H), 3.92 (q, 2H, J = 7.3 Hz), 6.90 (s, 1H), 7.13 (d, 2H, J = 7.9 Hz), 7.80 (d, 2H, J = 8.2 Hz) ppm; 13C-NMR (68 MHz, CDCl3 : C S2 = 1 : 1): δ 14.49, 21.46, 34.85, 66.00, 127.46, 129.22, 134.33, 137.32, 138.66, 139.35, 140.47, 141.16, 141.37, 142.01, 142.19, 142.45, 142.56, 142.91, 143.17, 144.00, 144.21, 144.75, 145.10, 145.16, 145.47, 145.63, 145.80, 146.05, 146.12, 146.21, 146.75, 147.45, 148.18, 149.96, 155.94 ppm. One sp3 carbon connected to the tosyl group may be ambiguous probably due to the rotation of tosyl group. HRMS (FAB-MS) was supported by the DFT calculations. These results were obtained by IR calculations as shown in ESI. The calculations were carried out with the B3LYP/6-31G(d) level, with o-DCB solvent parameter (IEFPCM). In the initial state, tosylazafulleroid 1 has four geometries,13 and the most stable isomer is 5-exo-1 (Fig. 2). Relative energies of the transition states were obtained as shown in Tables S1–S4† based on the total energies of initial 5-exo-1 and PhMgBr. In all TS calculations, only one imaginary frequency was obtained by IR calculations as shown in ESI.†

Acknowledgements

This work was supported by Grant-in-Aid for Young Scientist (B) (no. 24750039 and 15K21132) from Japan Society for the Promotion of Science (JSPS). The high regioselectivity was attained by the steric and coordination effect of the tosyl group. The Mg-coordinated intermediate was degraded into 1-alkyl/2-aminyl fullerene via [5,6] ring-closure and C–N bond scission. The 1,2-adducts are expected to undergo further derivatization owing to the presence of the tosylamino group. The reaction mechanism was supported by the DFT calculations. These results will provide significant information regarding regioselective heterodifunctionalization of fullerenes with the relatively rare 1,2-configuration.

Calculation procedure

DFT calculations were carried out with Gaussian 09. The full citation is in the ESI.† The calculations were carried out with the B3LYP/6-31G(d) level, with o-DCB solvent parameter (IEFPCM). In the initial state, tosylazafulleroid 1 has four geometries,13 and the most stable isomer is 5-exo-1 (Fig. 2). Relative energies of the transition states were obtained as shown in Tables S1–S4† based on the total energies of initial 5-exo-1 and PhMgBr. In all TS calculations, only one imaginary frequency was obtained by IR calculations as shown in ESI.†

Notes and references


25 As shown in Tables S1–S4,† Grignard reagents seem to coordinate oxygen rather than nitrogen of tosyl amide compounds due to the low N-basicity. Such results were found in the following papers. (a) B. Z. Lu, C. Senanayake, N. Li, Z. Han, R. P. Bakale and S. A. Wald, Org. Lett., 2005, 7, 2599–2602; (b) S. D. Kuduk, C. N. D. Marco, S. M. Pitzenberger and N. Tsou, Tetrahedron Lett., 2006, 47, 7107.

27 Product 3 has 1,4-ditolyl structure (C₂ symmetry) rather than 1,2-ditolyl product (C₂ᵥ symmetry), because the ¹³C NMR of 4 has ca. 30 peaks of sp² region similar to the previously obtained 1,4-ditolyl product by acidic arylation in ref. 11 (ESI†).