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

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Grignard reagents (RMgBr: R = Et, *p*-tolyl) selectively attacked the β-position of the bridgehead double bond of tosylazafulleroid 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 C_{60} [1–8] 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 (V_{oc}) of a fullerenyl photovoltaic cell due to the elevation of its LUMO level.[2,3] However, regiocontrolled sequential multi-functionalization is still a challenging topic because fullerene C_{60} 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 multiaddition has eagerly been explored using copper reagents,[2,5] 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 since 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 C_{60} 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 adjacent strained bridgehead double bonds. So far, regioselective reactions of azafulleroids have been reported for the [2 + 2] addition of singlet oxygen,[10] acidic arylation[11] and oxidation with peracids.[12] In addition to these electrophilic additions, the nucleophilic Grignard reaction, a useful reaction for the introduction of alkyl and aromatic groups with high yields,[13] can also be regioselective in the reaction of azafulleroid on account of the chelation of magnesium with the SO_2N unit of the tosylamino group.

Here, we report the regioselective additions of Grignard reagents to the β-position of the bridgehead double bond of tosylazafulleroid **1**, followed by [5,6] ring closure and C–N bond scission leading to 1,2-adducts.[14] As compared to the usual 1,4-adducts arising from Grignard[13d]/lithium[15] diaddition and from acid-catalyzed arylation,[11,16,17] the substituents of C_{60} 1,2-diadducts are limited to hydrogen and less bulky groups such as fluoride/chloride,[18] hydroxyl/ester,[17a,19] ethynyl,[20] methylene-connected alkyl,[21] cyano[19c,22] and azide group.[23] In order to explore the mechanistic preference for 1,2-addition, we have carried out the DFT calculations. For preparative extension, we also attempted the acid-catalyzed reaction 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 C_s-symmetric monoadducts **2a,b** *via* introduction of the R group at 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

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†Electronic supplementary information (ESI) available: HPLC and NMR charts, calculation results and full citation of calculation software. See DOI: 10.1039/c6ob00869k

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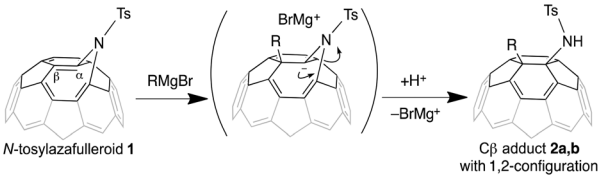
Table 1 Addition of alkyl/aryl Grignard reagents to tosylazafulleroid **1**



RMgBr	Temp./°C	Time/min	Yield of **2** [%]
R = Et[a] (3 equiv.)	25[c]	5	16 (**2a**)
	−70[d]	15	45 (**2a**)
p-Tolyl[b] (3 equiv.)	25[c]	10	91 (**2b**)
(5 equiv.)	25[c]	10	51 (**2b**)

[a] 3 M Et_2O solution. [b] 1 M THF solution. [c] *o*-Dichlorobenzene (*o*-DCB) solvent. [d] CH_2Cl_2 solvent.

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 Cα 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 Cα/Cβ additions of **1** with PhMgBr (in place of *p*-tolylMgBr) and EtMgBr were considered and clusterization of the Grignard reagent in the initial state was ignored.[24] Due to the S–N bond rotation and the Mg coordination of the TsN group,[25] four possible TS structures were examined for the Cα and Cβ additions, respectively. As seen in Fig. 1(a) and (b), regioselectivity for Cβ-addition can be explained by the DFT calculations (Tables S1–S4†). The smallest $\Delta E^{\ddagger}$ value was attained in TS(2-Cβ) 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-Cα) between Cα/Cβ would explain the high regioselectivity for aryl Grignard reagents, while the small difference (8 kJ mol^{-1}, *vs.* 1-Cα) for the less hindered ethyl reagent may result in the reduced Cβ-selectivity. As compared to the reaction of C_{60} ($\Delta E^{\ddagger}$ = +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.[10,11,26] The Cβ-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 Cβ in comparison with Cα.

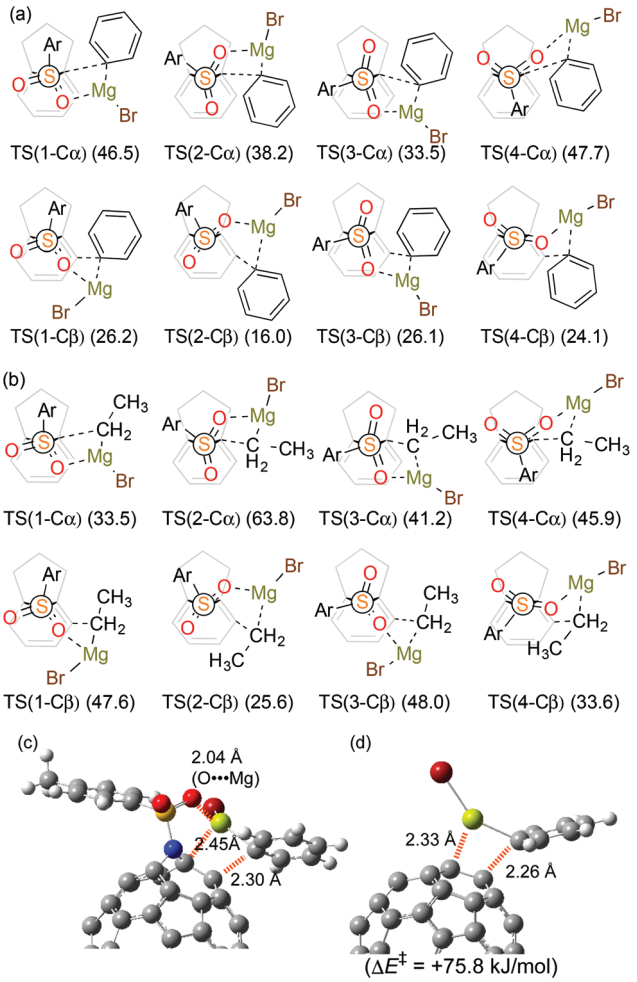


Fig. 1 TS energies (kJ mol^{-1}) with several configurations (top view) for reaction of **1** and (a) PhMgBr and (b) EtMgBr by B3LYP/6-31G(d)/IEFPCM(*o*-DCB). Circled-S means the stacking of S and N atoms. Ball and stick model of (c) TS(2-Cβ) with the lowest energy. (d) TS structure of C_{60} and PhMgBr.

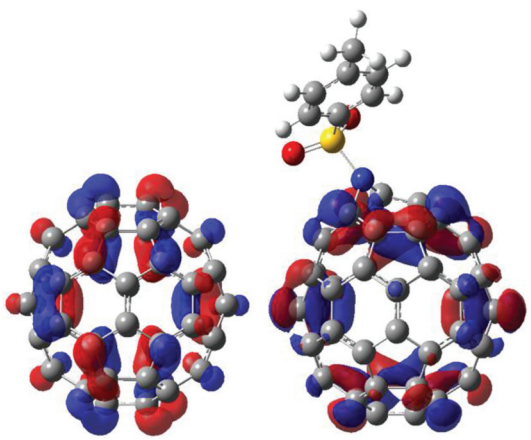


Fig. 2 LUMO orbital distribution of C_{60} (left, −3.14 eV) and **1** (right, −3.22 eV) calculated with B3LYP/6-31G(d)/IEFPCM (*o*-DCB).

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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-disubstituted 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, Cβ2···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

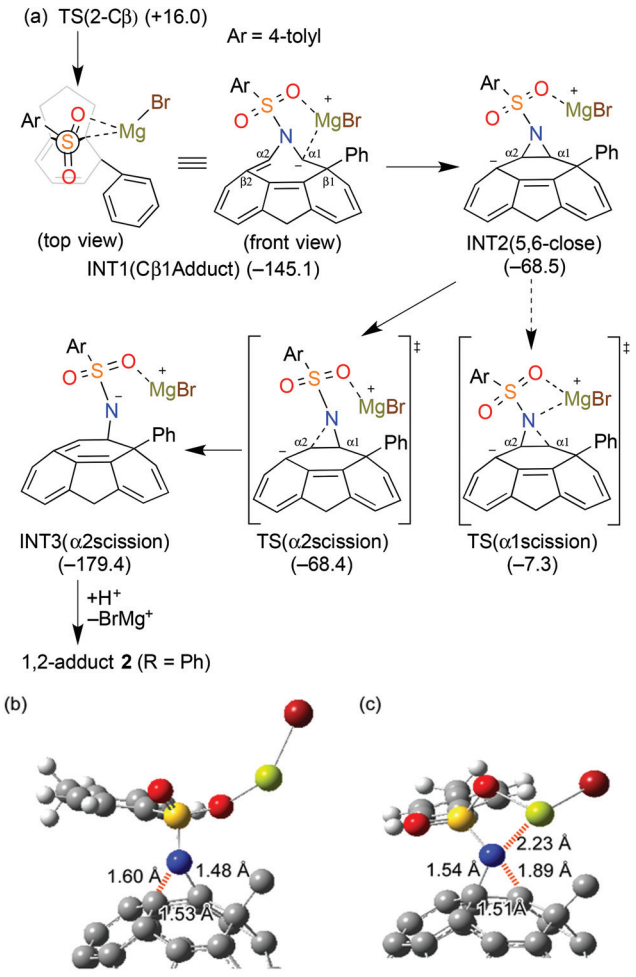


Fig. 3 (a) Plausible reaction pathway from Cβ-substituted intermediate INT1 to 1,2-adduct **2** (R = Ph) *via* 5,6-bond closure and N–C bond scission (energy: kJ mol^{-1}). (b) Cα2-cleaved and (c) Cα1-cleaved TS structures (phenyl group except for *ipso* carbon is omitted for clarity).

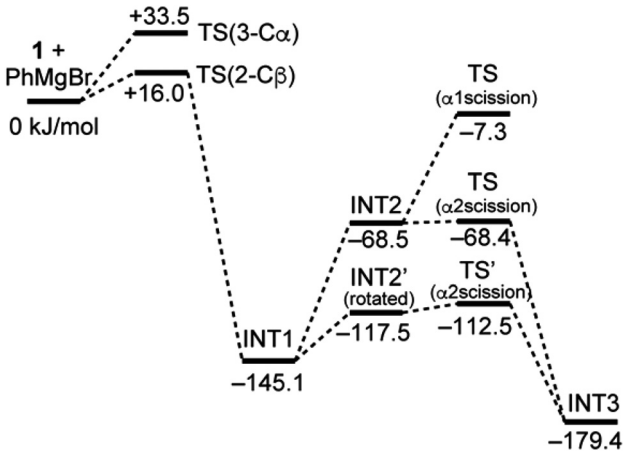
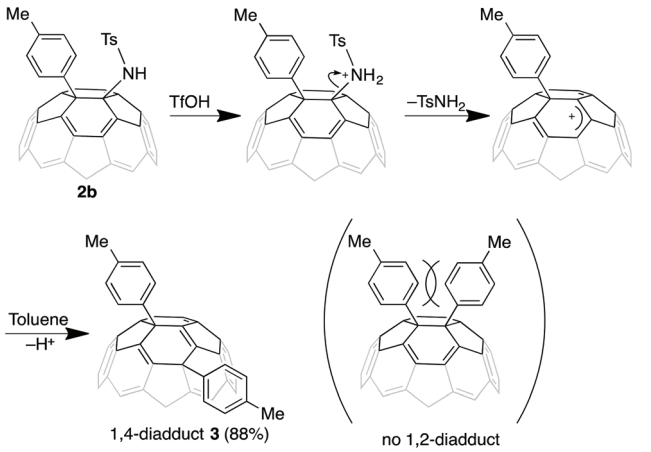


Fig. 4 Full energy diagram *via* Grignard reaction, 5,6-ring closure and CN bond scission. The detail of rotated pathway *via* INT2′ and TS′ is shown in ESI.†



Scheme 1

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,[11] 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 C_1 symmetry,[27] 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-

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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 Et_2O or 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 NH_4Cl solution and fractionated. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (CS_2/$CHCl_3$ eluent) to give product **2a,b** as a dark brown solid.

2a: ^{1}H-NMR (270 MHz, $CDCl_3 : CS_2 = 1 : 1$): 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; ^{13}C-NMR (68 MHz, $CDCl_3 : CS_2 = 1 : 1$): 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, 146.58, 147.45, 148.18, 149.96, 155.94 ppm. One sp^3 carbon connected to the tosyl group is ambiguous probably due to the rotation of the tosyl group. HRMS (FAB-MS) m/z calcd for $C_{69}H_{13}NO_2S^+$ [M^+]: 919.0662, found: 919.0646.

2b: ^{1}H-NMR (270 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.61 (s, 3H), 6.29 (s, 1H), 7.17 (d, 2H, J = 8.2 Hz), 7.67 (dd, 4H, J = 7.9, 8.2 Hz), 8.37 (d, 2H, J = 7.9 Hz) ppm; ^{13}C-NMR (68 MHz, $CDCl_3$): δ 21.44, 21.54, 74.96, 127.77, 129.36, 130.36, 131.17, 135.00, 136.97, 137.26, 138.56, 139.13, 140.08, 141.20, 141.48, 142.20, 142.29, 142.35, 142.65, 142.79, 143.18, 143.59, 144.54, 144.84, 144.90, 145.04, 145.27, 145.47, 145.64, 145.80, 146.08, 146.34, 146.39, 146.55, 146.80, 148.46, 149.38, 155.15 ppm. One sp^3 carbon connected to the tosyl group may be ambiguous probably due to the rotation of tosyl group. HRMS (FAB-MS) m/z calcd for $C_{74}H_{15}NO_2S^+$ [M^+]: 981.0818, found: 981.0827.

Acid-catalyzed substitution of 2b

The compound **2b** (10 mg) was dissolved in *o*-DCB (10 mL) containing 5 equiv. of toluene. A catalytic amount of trifluoromethanesulfonic acid (TfOH) was added at room temperature. After 30 minutes stirring, the reaction was quenched with water. The organic layer was separated, dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (CS_2 eluent) to give product **3** as a dark brown solid.

Compound **3**: ^{1}H-NMR (270 MHz, $CDCl_3 : CS_2 = 1 : 1$): δ 2.47 (s, 6H), 7.33(d, 4H, J = 8.2 Hz), 8.00(d, 4H, J = 8.2 Hz) ppm; ^{13}C-NMR (68 MHz, $CDCl_3 : CS_2 = 1 : 1$): δ 21.06, 62.38, 128.11, 128.89, 137.29, 137.53, 137.56, 137.83 (2 × 2C), 138.78, 142.18, 142.51, 142.56, 142.67, 143.09, 143.14, 143.82, 143.88, 143.94, 144.17, 144.31 (2 × 2C), 144.70, 144.82, 144.97, 145.18, 145.49, 146.77, 146.91, 146.95, 147.05, 148.47, 148.60, 151.06, 156.77, 156.82 ppm.

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,[12] 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

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