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Graphical Abstract

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Regio/diastereo-controls of the Bingel-type biscyclopropanation of [60]fullerene by using bismalonates with a Tröger base analogue-derived tether

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Abstract—Four kinds of bismalonates tethered with a Tröger base derivative were synthesized and used for the double Bingel reaction of [60]fullerene. The regio/diastereoselectivities of the reaction were highly influenced by the structure of the Tröger base derivatives. Heteroaromatic analogues of the Tröger base were found to be applicable as the core of the tether.

The regio- and diastereo-controls of the bifunctionalization of [60]fullerene (C_{60}) have attracted considerable attention, because the bisadducts of C_{60} have been increasingly finding widespread applications in the construction of supramolecular advanced materials.¹ The tether-directed remote functionalization of C_{60} has been proved a versatile and reliable strategy to prepare bifunctionalized C_{60} regio- and stereoselectively.² Since the first report of this elegant approach has appeared, several motifs have been utilized as the core part of the tether, of which the length and shape are known to directly affect the addition pattern.³ In addition, donor–acceptor interaction between the tether and C_{60} has been considered to be an additional factor for the regio- and stereo-controls of C_{60} bifunctionalizations, which has been found through our investigation on the Bingel-type biscyclopropanation, controlled by tethers having a benzene derivative with electron-donating groups as a core.⁴ This result prompted us to develop a new core for the regio- and diastereoselective, tether-directed bifunctionalization of C_{60} .

Among possible candidates as the scaffolds of tethers, the derivatives of the Tröger base were considered to be attractive (Scheme 1).^{5,6} The molecular modeling and X-ray crystallographic studies revealed that the Tröger base possessed a concave structure composed of two aromatic rings.^{5d,5e} Because the curvature of its shape seemed near to that of the surface of C_{60} , the two anilino groups were

expected to efficiently associate with C_{60} via donor–acceptor interaction. Recently, Sergeyev and Diederich reported the application of Tröger base derivatives for the Bingel-type biscyclopropanation to obtain *trans*-1, *trans*-2, and *trans*-4 bisadducts with excellent regioselectivity.⁷

We have independently attempted to show the utility of Tröger base derivatives for the tether-directed double Bingel reaction, especially focusing on the wide diversity of the synthetically available Tröger base derivatives with heteroaromatic rings.⁸ From a synthetic viewpoint, the introduction of the derivatives with heteroaromatic rings has a significant advantage; some heteroaromatic rings can be easily and regioselectively modified with a hydroxycarbonyl, alkoxycarbonyl, and/or formyl group, which is readily converted to a hydroxymethyl group by simple reduction, in sharp contrast with the fact that available hydrocarbon aromatic amines with a hydroxymethyl group (or an equivalent functionality) are strictly limited, although such amines are indispensable for the construction of bismalonates tethered with a Tröger base derivative. Furthermore, the heteroatom(s) introduced in the ring system should influence the electron density and/or perturbation of the aromatic ring, which is expected to bring some effect on the regio/diastereoselectivities of the bifunctionalization reaction. Here we report the results of the tether-directed double Bingel reaction of C_{60} , using various Tröger base derivatives as the tether core.

Keywords: bifunctionalization; Bingel reaction; fullerene; heteroaromatic ring; template synthesis; Tröger base.

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We initially investigated the effect of the angle between the two aromatic rings of Tröger base derivatives. Fortunately, Tröger base analogues with a smaller bent angle are easily accessible by replacing the methylene bridge, connecting the two nitrogens, with an ethylene bridge.⁹ Energy-minimized calculations indicated that the bent angles are 100 and 80 ° for the methylene-bridged and ethylene-bridged compounds, respectively. Therefore, the corresponding bismalonates, with a normal Tröger base core (**1a**) and with an ethylene-bridged core (**2a**) were synthesized (Scheme 2) and applied to the double Bingel reaction. According to the literature, 4-bromoaniline (**5**) was allowed to react with paraformaldehyde in the presence of trifluoroacetic acid to afford **6** (30% yield).^{10a} As the fundamental skeleton of **2a**, the dibromide **7** was synthesized from **6** by the reaction with 1,2-dibromoethane (39% yield).⁹ Lithiations of the dibromides **6** and **7**, followed by the treatment with DMF, gave the corresponding dialdehydes **8** and **10** (68 and 53% yields), respectively.^{10b} The formyl groups of **8** and **10** were reduced with ⁿBu₃SnH (61 and 51% yields),^{10c} and the resultant diols **9** and **11** were condensed with ethyl malonyl chloride to afford **1a** and **2a**, respectively (85 and 64% yields).

The reactions of **1a** and **2a** with C₆₀ were performed in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and iodine according to the reported method (Scheme 1).^{11,12} From the reaction mixture, bisadducts were isolated by chromatographic separation, of which the addition pattern and the relative configuration of the bridge-head carbons were identified by UV/Vis and NMR spectroscopies.^{13,14,15} The results of the biscyclopropanations of C₆₀ with **1a** and with **2a** revealed that the bent angle of the traditional Tröger base is capable of controlling the biscyclopropanation reaction. The reaction of **2a** with C₆₀ proceeded with unsatisfactory selectivity to afford a mixture of several bisadducts. As the main product, the isomer with the highest polarity was collected, of which the UV/Vis absorption spectrum was consistent with the pattern of *e*-bisadducts (*e*-**2a**, 18% yield).¹⁵ However, the *e*-bisadduct thus obtained was likely to be a mixture of the diastereoisomers with respect to the stereochemistry of the bridge-head carbon(s).¹⁴ The obtained sample showed a complicated ¹H NMR spectrum, although the MALDI-TOF-MS and UV/Vis spectroscopy indicated the successful isolation of the *e*-bisadduct. In sharp contrast, the tether with a normal Tröger base core attained good regio- and diastereoselectivities. When the reaction of **1a** with C₆₀ was conducted in the same procedure, the *trans*-2 bisadduct with C₂ symmetry (*t*₂-**1b**) and the *e* bisadduct with C₁ symmetry (*e*-**1b**) were isolated (46 and 11% yields, respectively).¹⁵ In spite of the inherent chirality of *trans*-2 bisadducts, *t*₂-**1b** showed a quite simple ¹H NMR spectrum, indicating the diastereoselective formation of this isomer. Furthermore, **1a** also controlled the chirality of *e*-**1b**, with respect to the relative configuration of the bridge-head carbons of the cyclopropane rings. Concerned with the relative orientation of the ethoxycarbonyl groups, the *out-out* isomer was assigned for *e*-**1b**. For the *out-out* isomer of the *e*-bisadduct, two diastereomers are possible in theory,

but only one of them was selectively generated, which was confirmed by ¹H NMR spectroscopy.¹⁴ Although thus observed good regio- and diastereoselectivities were in good agreement with the results reported by Diederich *et al.*, our reaction conditions would be rather suitable compared with their conditions from a practical viewpoint; the yields of the *t*₂-**1b** and *e*-**1b** were highly improved without the deterioration of the regio/diastereoselectivities.⁷

i) (H₂CO)_n, TFA, 0 °C; ii) BrCH₂CH₂Br, Li₂CO₃, DMF, 105 °C; iii) ⁿBuLi, THF, -78 °C, 15 min, then DMF/THF, -78 °C to RT; iv) ⁿBu₃SnH, MeOH, reflux; v) EtOCOCH₂COCl, Et₃N or Pyridine, THF, RT; vi) KOH^{aq}, reflux, then (COOH)₂, ⁿPrOH; vii) HCHO^{aq}, HCl^{aq}, MeOH or EtOH, RT; viii) LiAlH₄, THF, RT; ix) Pd/C, H₂, MeOH, RT.

Taking into account the donor–acceptor interaction between C₆₀ and the tether core, further improvement in regio/diastereoselectivity might be expected by replacing the two benzene rings with heteroaromatic rings. Although various Tröger base derivatives are synthetically available, we decided to test thiophene and benzothiophene analogues, **3a** and **4a**, as the scaffolds of tethers in the biscyclopropanation reaction, because the relatively electron-rich five-membered ring and/or the lone pair of the sulfur atom might be work as electron-donating unit(s).¹⁶ The Tröger base derivatives **3a** and **4a** were prepared from ethyl 2-(3-aminothiophene)carboxylate (**12**) and methyl 2-(5-nitrobenzo[*b*]thiophene)carboxylate (**17**), respectively, through procedures similar to those for the preparation of

1a and **2a** with some modifications (Scheme 2).^{9,18,19} Interestingly, the double Bingel reaction of C₆₀ with **3a** proceeded with excellent regioselectivity. From the reaction mixture, two kinds of bisadducts were isolated (22 and 1%, respectively). The major product was assigned to be the *trans*-2 bisadduct with C₂ symmetry (*t*₂^{major}-**3b**). The addition pattern of the minor product (*t*₂^{minor}-**3b**) could be deduced only on the basis of UV/Vis and ¹H NMR spectroscopies;¹⁵ the minor product gave an absorption spectrum almost identical to that of *t*₂^{major}-**3b**, and its ¹H NMR spectrum agreed with the assumption that it is C₂ symmetry. Therefore, *t*₂^{minor}-**3b** was most likely to be the diastereoisomer of *t*₂^{major}-**3b**, with respect to the inherent chirality of the *trans*-2 bisadduct. Although precise mechanism should be investigated hereafter, good regio- and diastereoselectivities thus observed might be a result of (i) the donor–acceptor interaction between the electron-rich thiophene rings and C₆₀ and/or (ii) suitable arrangement of the two malonate moieties owing to the five-membered structure of the thiophene rings. Contrary to this, such an excellent selectivity was not observed in the double Bingel reaction of the benzothiophene analogue **4a** with C₆₀. From the reaction mixture, the *trans*-2 bisadduct with C₂ symmetry (*t*₂-**4b**) and the *trans*-4 bisadduct with C₁ symmetry (*t*₄-**4b**) were isolated (20 and 5% yields, respectively).¹⁵ Due to the two large benzothiophene units involved in **4a**, the distance between the two rings was likely to be too far to co-operatively interact with C₆₀. Worth to note is the formation of the *trans*-4 bisadduct; despite the relatively long distance between the two malonate moieties, **4a** gave the *trans*-4 bisadduct, in which the two reaction sites were near to each other, compared with those between the *e* position and between *trans*-1–3 positions. Considering the length and rigidity of the linker between the two cyclopropane rings of **4b**, the ethoxycarbonyl residues on the bridge-head carbons were most likely to be arranged in an *in-in* orientation.

In conclusion, various Tröger base derivatives were used for the tether-directed remote bifunctionalization of C₆₀, and some of them showed a good to excellent regio- and diastereoselectivities. In order to achieve good selectivity, the bent angle of the Tröger base core and the choice of the aromatic rings in the framework are critical factors. Worth to note is that the bifunctionalization reaction with **3a** possessing two thiophene rings afforded the *trans*-2 bisadduct with excellent selectivity. Considering the wide diversity of the accessible derivatives, the utilization of Tröger base analogues with heterocyclic aromatic rings as the tether-core is expected to be an efficient method for the facile regio/stereo-controls of the bifunctionalization of C₆₀.

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- Representative procedure of the reactions of **1a–4a** with C₆₀: A toluene solution of C₆₀ (36 mg, 0.050 mmol), **1a** (25.5 mg, 0.050 mmol), and iodine (25 mg, 0.10 mmol) was thoroughly degassed and stirred at room temperature for 1h. To the reaction mixture was added dropwise a degassed solution of DBU (31.0 mg, 0.20 mmol) in toluene, and the mixture was stirred at room temperature for 3h. The resulting mixture was concentrated under reduced pressure, and subjected to a silica gel column chromatography. Elution with ethyl acetate/toluene (0:100 to 20:80, v/v) afforded *t*₂-**1b** (28 mg, 46%) and *e*-**1b** (7 mg, 11%).
- Identification of the addition pattern of **1b–4b**: The UV/Vis spectra of the synthesized bisadducts, *e*-**1b**, *e*-**2b**, *t*₂-**1b**, *t*₂^{major}-**3b**, *t*₂^{minor}-**3b**, *t*₂-**4b**, and *t*₄-**4b**, were essentially identical to those reported for the corresponding isomers of the bis(diethyl malonate) adduct of C₆₀. For the absorption spectra of the authentic bisadducts, see (a) I. Sucholeiki, V. Lynch, L. Phan, S. S. Wilcox, *J. Org. Chem.* **1988**, *53*, 98; (b) C. S. Wilcox, *Tetrahedron Lett.* **1985**, *26*, 5749. The ¹H and ¹³C NMR spectra of the synthesized bisadducts agreed with the symmetry deduced on the basis of the absorption spectra. C₂ symmetry: *t*₂-**1b**, *t*₂^{major}-**3b**, *t*₂^{minor}-**3b**, and *t*₂-**4b**. C₁ symmetry: *e*-**1b** and *t*₄-**4b**.
- Assignment of the configuration of the bridge-head carbons in **1b–4b**: The tether-directed double Bingel reaction of C₆₀ can afford several diastereoisomers with respect to the relative orientation of the ethoxycarbonyl groups at the bridge-head carbons (*in-in*, *in-out*, *out-out*). The ¹H NMR spectra of *e*-**1b**, *t*₂-**1b**, *t*₂^{major}-**3b**, *t*₂^{minor}-**3b**, *t*₂-**4b**, and *t*₄-**4b** indicated the successful isolation of single racemates.

- Considering the distance of the two malonates in **1a–4a**, the *out-out* configuration was assigned for *e*-**1b**, *t*₂-**1b**, *t*₂^{major}-**3b**, *t*₂^{minor}-**3b**, and *t*₂-**4b**. For *t*₄-**4b**, see text.
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