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Unexpected switch in regioselectivity of tether-directed Bingel-type biscyclopropanations depending on the leaving groups at tethered active methylene moieties† ‡

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Received (in Cambridge, UK) 18th November 2002, Accepted 13th December 2002
First published as an Advance Article on the web 9th January 2003

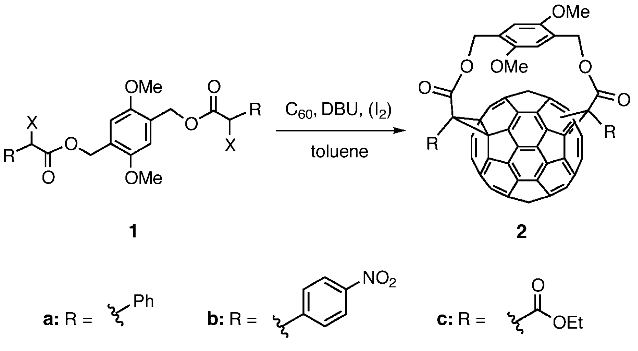
The regioselectivity of tether-directed Bingel-type biscyclopropanations of [60]fullerene was switched depending on the leaving groups at tethered active methylene moieties; the reactions of [60]fullerene with unhalogenated tethered bis(active methylene) derivatives/I_2 and with brominated derivatives in the presence of 1,7-diazabicyclo[5.4.0]undec-7-ene gave *trans*-4-adducts predominantly, while the reactions with chlorinated derivatives afforded *equatorial*-adducts almost exclusively.

The regio- and diastereo-controls for the bifunctionalization of [60]fullerene (C_{60}) have attracted considerable attention, since bisadducts of C_{60} have been increasingly finding widespread applications in the construction of supermolecular advanced materials.[1] The elegant synthetic approaches for the bifunctionalization of C_{60} can be roughly classified into two strategies, stepwise bisadditions *via* reversible template-directed activations[2] and tether-directed remote bifunctionalizations.[3] In particular, the tether-directed Bingel-type biscyclopropanation (the double Bingel reaction) of C_{60} with bifunctional compounds having two active methylene moieties is one of the most useful methods, because it is a versatile and simple method for the preparation of various covalently bonded fullerenobisadducts with high regio- and/or diastereoselectivity.[4] In order to obtain different kinds of regio- and/or diastereoisomeric bisadducts, however, this approach generally requires another tether different in length. We report herein that the regioselectivity of tether-directed Bingel-type biscyclopropanations is highly dependent on the leaving groups at tethered active methylene moieties.

In the course of our research on the synthesis of [60]fullerene pearl-necklace polyamides,[5] a regioisomerically and diastereomerically pure [60]fullerenobis(acetic acid) derivative $[C_{60}(>CRCOOH)_2]$ was greatly required to be prepared in acceptable yield as a dicarboxylic acid component. Thus, we carried out the reaction of C_{60} with the tethered bis(phenylacetate) derivative **1a-H**, having a π-electron-rich aromatic ring as a tether,[6] in the presence of I_2 and 1,7-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at rt, according to a general synthetic protocol. The Bingel-type biscyclopropanation, however, did not proceed at all when the reaction was carried out at rt for 24 h (Table 1, run 1), or even at 70 °C for one week, presumably due to the lower acidity of the methylene protons of the phenylacetate moieties in **1a-H** than those of bis(ethyl malonate) derivatives, which are generally used in Bingel-type biscyclopropanations. In contrast, the reactions of C_{60} with the **1a-H** derivatives having halo groups at the α-positions of the phenylacetate moieties (**1a-Br** and **1a-Cl**) under similar reaction conditions gave the biscyclopropanated product **2** in 73 and 50% yields, respectively (runs 2 and 3). To our surprise, a different regioisomer was, however, formed as a major product in each reaction; **1a-Br** mainly yielded the corresponding *trans*-4-biscyclopropanated product **t-2a**, whereas **1a-Cl** gave predominantly the *equatorial*-biscyclopropanated product **e-2a**.§ This unexpected reaction behavior suggests that the regioselectivity of tether-directed Bingel-type biscyclopropanations can be controlled upon changing only the leaving groups of tethered bis(active methylene) derivatives. This finding promoted us to further investigate the Bingel-type biscyclopropanations of various tethered bis(active methylene) derivatives.

As a result, the behavior and product-distribution of the reactions of the bis(4-nitrophenylacetate) derivatives **1b** and the bis(ethyl malonate) derivatives **1c** were similar to those of **1a**; the reactions of C_{60} with **1b-Br** and **1c-Br** gave the *trans*-4-biscyclopropanated **t-2b** and **t-2c**, respectively, as major products (runs 5 and 8), while the reactions with **1b-Cl** and **1c-Cl** provided almost only the *equatorial*-biscyclopropanated **e-2b** and **e-2c**, respectively (runs 6 and 9). For the reaction in the presence of I_2 and DBU, no reaction proceeded with either **1b-H** or **1a-H**. In contrast, **1c-H** in the presence of I_2 and DBU exhibited somewhat different behavior (run 7); **1c-H** afforded the *trans*-4-biscyclopropanated **t-2c** exclusively. These results clearly demonstrate that the product-distribution for **t-2** and **e-2** is governed by the leaving groups at the tethered active methylene moieties.

Table 1 Bingel-type biscyclopropanation of **1**[a]



Run	Substrate	Yield of **t-2** (%)	Yield of **e-2** (%)
1	**1a-H**[b]	—	—
2	**1a-Br**	66	7
3	**1a-Cl**	trace	50
4	**1b-H**[b]	—	—
5	**1b-Br**	44	24
6	**1b-Cl**	trace	59
7	**1c-H**[bc]	56	trace
8	**1c-Br**	28	25
9	**1c-Cl**	trace	65

[a] The reaction of 0.1 mmol of C_{60}, 0.1 mmol of **1**, and 0.6 mmol of DBU was carried out in 72 mL of toluene at rt for 24 h. [b] The reaction was carried out in the presence of 0.3 mmol of I_2. [c] Ref. 6.

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† This paper is dedicated to Emeritus Professor Soichi Misumi on the occasion of his 77th birthday.

‡ Electronic supplementary information (ESI) available: NMR, IR, UV/Vis and mass spectroscopies of **t-2a** and **e-2a**. See http://www.rsc.org/suppdata/cc/b2/b211337f/

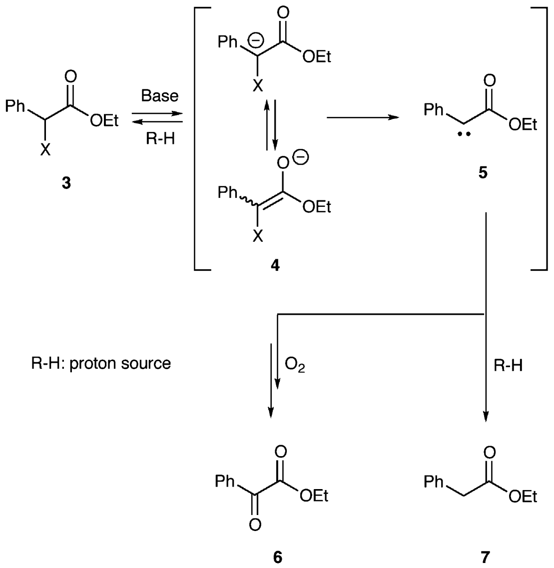
DOI: 10.1039/b211337f

For the explanation of this behavior, the difference in *E*/*Z* ratio was first considered to be possible for the intermediate enolates generated from **1**. No distinct difference, however, was observed in the *E*/*Z* ratio between the ketene silyl acetals, which were obtained from the model compounds **3-Br** and **3-Cl** through the intermediacy enolates **4-Br** and **4-Cl**, respectively, (Scheme 1) upon trapping the enolates with chlorotrimethylsilane. On the basis of these model reactions, the possibility of the difference in *E*/*Z* ratio between the enolates formed from **1** would be excluded for the present switch in regioselectivity.

The double Bingel reactions of C_{60} with the model compounds **3-Br** and **3-Cl** under similar reaction conditions to those of tethered **1** gave mainly the *equatorial*-bisadduct (*ca*. 40% yields), accompanying the formation of the *trans*-4-bisadduct (*ca*. 10% yields). This reaction behavior means that the *equatorial*-position is the most reactive in the second Bingel reaction, as was observed for the reaction with diethyl α-bromomalonate.[7] In contrast, the steric repulsion between the tether part and the fullerene core in the *equatorial*-adducts **e-2** seems to be rather larger than that of the *trans*-4-adducts **t-2** by an examination with CPK molecular models. These observations led us to surmise that the *equatorial*-adducts **e-2** and *trans*-4-adducts **t-2** would be, respectively, kinetically and thermodynamically favorable.

In an experiment in which the model compound **3-Cl** was treated with DBU for 24 h, followed by quenching with water, the starting material was recovered in quantitative yield, while under similar reaction conditions **3-Br** and **3-H**/I_2 gave the oxidized and reduced compounds **6** and **7** (7 and 9%, respectively, for **3-Br**; 8 and 12%, respectively for **3-H**/I_2) along with a large amount of a mixture of unidentified by-products, probably produced by the side-reactions with remaining DBU, and a small amount of the starting material. Moreover, the yields of the oxidized and reduced products were obviously improved, when the reactions of **3-Br**/DBU and **3-H**/I_2/DBU were carried out under an oxygen atmosphere. The quantitative recovery of the starting material upon treatment with DBU, followed by quenching with water, indicates that the reactive species would be a carbanion in the reaction of **3-Cl**/DBU. On the other hand, the formation of the oxidized and reduced compounds strongly suggests that the reactive species would be a carbene in the reactions of **3-Br**/DBU and **3-H**/I_2/DBU,[8] although the self-dimerization of the carbene was not observed in our system, probably owing to the very low concentration (0.1 mmol of the substrates in 72 mL of toluene).[9]

On the basis of these model reactions, it is strongly suggested that the main reactive intermediates are carbanions in the reactions of **1-Cl**/DBU, while the reactive intermediates are carbenes (carbenoids) in the reactions of **1-Br**/DBU and **1-H**/I_2/DBU. Different intermediates gave different regioisomers; the carbanions and carbenes would give the kinetic products **e-2** and the thermodynamic products **t-2**, respectively. Thus, the nature of the leaving groups as well as that of the tether part[4] plays an important role for the control of the regioselectivity of tether-directed Bingel-type biscyclopropanations.



Scheme 1 Model reactions for investigating the intermediates

This work was financially supported by the JSPS (the Future Program).

Notes and references

§ A representative procedure for the preparation of bisadducts **t-2a** and **e-2a**: to a solution of C_{60} (72 mg, 0.1 mmol) and **1a-Br** (59.2 mg, 0.1 mmol) dissolved in dry toluene (72 mL) was added dropwise a toluene solution (0.4 mL) of DBU (91.3 mg, 0.6 mmol) under argon. After the solution was stirred at rt for 24 h under argon, the mixture was directly chromatographed on silica gel (eluent: hexane to chloroform and then dichloromethane) to give biscyclopropanated **t-2a** and **e-2a**.‡

1 (*a*) K. M. Kadish and R. S. Ruoff, *Fullerenes: chemistry, physics, and technology*, Wiley-Interscience, New York, 2000; (*b*) F. Diederich and R. Kessinger, *Acc. Chem. Res.*, 1999, **32**, 537; (*c*) F. Diederich and C. Thilgen, *Science*, 1996, **271**, 317; (*d*) A. Hirsch, *The chemistry of the fullerenes*, Thieme, Stuttgart, 1994.

2 (*a*) W. Qian and Y. Rubin, *Angew. Chem., Int. Ed.*, 2000, **39**, 3133; (*b*) W. Qian and Y. Rubin, *Angew. Chem., Int. Ed.*, 1999, **38**, 2356; (*c*) T. Habicher, J.-F. Nierengarten, V. Gramlich and F. Diederich, *Angew. Chem., Int. Ed.*, 1998, **37**, 1916; (*d*) R. Schwenniger, T. Müller and B. Kräutler, *J. Am. Chem. Soc.*, 1997, **119**, 9317; (*e*) P. Timmerman, L. E. Witschel, F. Diederich, C. Boudon, J.-P. Gisselbrecht and M. Gross, *Helv. Chim. Acta*, 1996, **79**, 6; (*f*) I. Lamparth, C. Maichle-Mössner and A. Hirsch, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1607; (*g*) A. Hirsch, I. Lamparth, T. Grösser and H. R. Karfunkel, *J. Am. Chem. Soc.*, 1994, **116**, 9385.

3 (*a*) Y. Nakamura, A. Asami, S. Inoue, T. Ogawa, M. Kikuyama and J. Nishimura, *Tetrahedron Lett.*, 2000, **41**, 2193; (*b*) T. Ishi-i, K. Nakashima, S. Shinkai and A. Ikeda, *J. Org. Chem.*, 1999, **64**, 984; (*c*) F. Cardullo, P. Seiler, L. Isaacs, J.-F. Nierengarten, R. F. Haldimann, F. Diederich, T. Mordasini-Denti, W. Thiel, C. Boudon, J.-P. Gisselbrecht and M. Gross, *Helv. Chim. Acta*, 1997, **80**, 343; (*d*) L. Isaacs, F. Diederich and R. F. Haldimann, *Helv. Chim. Acta*, 1997, **80**, 317; (*e*) R. F. Haldimann, F.-G. Klärner and F. Diederich, *Chem. Commun.*, 1997, 237; (*f*) C. K.-F. Shen, H.-h Y. Yu, C.-G. Juo, K.-M. Chien, G.-R. Her and T.-Y. Luh, *Chem. Eur. J.*, 1997, **3**, 744; (*g*) H. Isobe, H. Tokuyama, M. Sawamura and E. Nakamura, *J. Org. Chem.*, 1997, **62**, 5034; (*h*) M. Taki, S. Sugita, Y. Nakamura, E. Kasashima, E. Yashima, Y. Okamoto and J. Nishimura, *J. Am. Chem. Soc.*, 1997, **119**, 926; (*i*) F. Cardullo, L. Isaacs, F. Diederich, J.-P. Gisselbrecht, C. Boudon and M. Gross, *Chem. Commun.*, 1996, 797; (*j*) L. Isaacs, P. Seiler and F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1466; (*k*) L. Isaacs, R. F. Haldimann and F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2339.

4 (*a*) G. A. Burley, P. A. Keller, S. G. Pyne and G. E. Ball, *J. Org. Chem.*, 2002, **67**, 8316; (*b*) J.-P. Bourgeois, L. Echegoyen, M. Fibbioli, E. Pretsch and F. Diederich, *Angew. Chem., Int. Ed.*, 1998, **37**, 2118; (*c*) E. Dietel, A. Hirsch, E. Eichhorn, A. Rieker, S. Hackbarth and B. Röder, *Chem. Commun.*, 1998, 1981; (*d*) J.-F. Nierengarten, T. Habicher, R. Kessinger, F. Cardullo, F. Diederich, V. Gramlich, J.-P. Gisselbrecht, C. Boudon and M. Gross, *Helv. Chim. Acta*, 1997, **80**, 2238; (*e*) P. R. Ashton, F. Diederich, M. Gómez-López, J.-F. Nierengarten, J. A. Preece, F. M. Raymo and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1448; (*f*) J.-F. Nierengarten, V. Gramlich, F. Cardullo and F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2101.

5 L. X. Xiao, K. Kitazawa and K. Saigo, *Fullerene Sci. Technol.*, 2000, **8**, 531 and references cited therein.

6 J.-Y. Zheng, S. Noguchi, K. Miyauchi, M. Hamada, K. Kinbara and K. Saigo, *Fullerene Sci. Technol.*, 2001, **9**, 467.

7 A. Hirsh, I. Lamparth and H. R. Karfunkel, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 437.

8 (*a*) G. A. Burley, P. A. Keller, S. G. Pyne and G. E. Ball, *Chem. Commun.*, 2000, 1717; (*b*) J.-F. Nierengarten and J.-F. Nicoud, *Tetrahedron Lett.*, 1997, **38**, 7737.

9 (*a*) B. C. Gilbert, D. Griller and A. S. Nazran, *J. Org. Chem.*, 1985, **50**, 4738; (*b*) W. Kirms, *Carbene Chemistry*, Academic press, New York, 1964; (*c*) K. Ishiguro, Y. Hirano and Y. Sawaki, *J. Org. Chem.*, 1988, **53**, 5397.