CLAIMS

1. A method for producing a heteromultimer, comprising the steps of:
a) providing a homo variant of first polypeptides each having a first antigen-binding activity and comprising an Fc region;
b) providing a homo variant of second polypeptides each having a second antigen-binding activity different from the first antigen-binding activity and comprising an Fc region;
c) incubating the homo variant of the first polypeptides and the homo variant of the second polypeptides together under a reducing condition that allows cysteines in hinge regions to cause disulfide bond isomerization; and
d) obtaining a heteromultimer comprising the first and second polypeptides, wherein
an amino acid at EU numbering position 397 in a CH3 region contained in the Fc region of the first and/or second polypeptide is substituted
wherein the amino acid at EU numbering position 397 is an amino acid having a bulky side chain or an amino acid having a branched side chanin and is substituted to Met (M), Phe (F), or Tyr (Y).

2. The method according to claim 1, wherein in the first and/or second polypeptide,

the amino acid at EU numbering position 392 is substituted to Asp (D), Glu (E), Thr (T), Val (V), or Ile (I).

3. The method according to claim 1 or 2, wherein in the first and/or second polypeptide, the amino acid at EU numbering position 397 is substituted to Phe (F) or Tyr (Y).

4. The method according to any one of claims 1 to 3, wherein the steps a) and b) are carried out by mixing a cell line producing the homo variant of the first polypeptides with a cell line producing the homo variant of the second polypeptides, and the step c) is carried out in the culture supernatant.

5. The method according to any one of claims 1 to 4, wherein the heteromultimer is a multispecific antibody or a hetero-Fc fusion protein.

6. The method according to any one of claims 1 to 5, wherein the heteromultimer is a bispecific antibody.

7. The method according to any one of claims 1 to 6, wherein the step c) described in claim 1 or claim 11 involves contact with a reducing agent.

8. The method according to claim 7, wherein the step c) involves the addition of an active substance selected from the group consisting of glutathione, L-cysteine, dithiothreitol, β-mercapto-ethanol, TCEP, and 2-MEA.

9. The method according to claim 8, wherein the step c) involves the addition of an active substance selected from glutathione and 2-MEA.