Gold Catalysis

Gold-Catalyzed Regiospecific Annulation of Unsymmetrically Substituted 1,5-Diyynes for the Precise Synthesis of Bispentalenes

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Abstract: Precise control of the selectivity in organic synthesis is important to access the desired molecules. We demonstrate a regiospecific annulation of unsymmetrically substituted 1,2-di(arylthynyl)benzene derivatives for a geometry-controlled synthesis of linear bispentalenes, which is one of the promising structures for material science. A gold-catalyzed annulation of unsymmetrically substituted 1,2-di(arylthynyl)benzene could produce two isomeric pentalenes, but both electronic and steric effects on the aromatics at the terminal position of the alkyne prove to be crucial for the selectivity; especially a regiospecific annulation was achieved with sterically blocked substituents; namely, 2,4,6-trimethyl benzene or 2,4-dimethyl benzene. This approach enables the geometrical control of annulation of linear bispentalenes from 1,2,4,5-tetraethynylbenzene or 2,3,6,7-tetraethynyl-naphtalene. Moreover, the annulation of a series of tetrabenzenes with a different substitution pattern regioselectively provided the bispentalene scaffolds. A computational study revealed that this is the result of a kinetic control induced by the bulky NHC ligands.

Introduction

Antiaromatic molecules have received much attention due to unique optoelectronic properties. Pentalene as well as the structurally similar indeno[1,2-b]fluorene is one of the important core structures for material science. Due to the low stability of the pure pentalene core, various syntheses of dibenzo[α,ε]-pentalenes, which are stabilized by the fused aromatic moieties, have been developed. The properties of pentalene are of high interest for organic semiconductors. Especially, π-extended pentalenes prove to act as p- or n-type organic transistors, although tuning optoelectronic properties by the introduction of functional groups are still desirable for higher performance. Therefore, the development of modular synthetic methods to access polycyclic π-extended pentalenes is a promising research topic.

Homogeneous gold catalysis has received much attention, and due to the mild carbophilic Lewis acidity of the gold catalyst, the field majorly contributed to the intensive development of nucleophilic addition reactions to unsaturated carbon–carbon multiple bonds. For instance, the gold-catalyzed annulation of diyne compounds enabled the synthesis of extended π-conjugated compounds, such as azahelicene, polycyclic indole and benzothiophen derivatives. Our recent work also contributed to the gold-catalyzed synthesis of dibenzo[α,ε]-pentalene and quinoxaline/phenazine-fused pentalene derivatives from 1,5-diynes. Moreover, the gold catalyst led to both U-shaped and S-shaped bispentalenes from the readily available tetra(arylthynyl)benzenes and naphtalenes, albeit fortunately those mixtures could be separated (Scheme 1, top). During that study, the naphtalene-based linear bispentalene (S-shaped) was found to be a highly suitable scaffold for transistor applications. In these symmetric tetrabenzenes, however, the chemoselectivity towards U-shaped and S-shaped bispentalenes is not controlled. Unsymmetrically substituted diynes or tetrabenzenes as substrates could be a method to selectively synthesize specific isomers, still it is unknown whether the selectivity will be pronounced enough to deliver only one
Results and Discussion

During the annulation of a symmetric 1,5-diyne, one alkyne acts as a nucleophile and the other alkyne as the electrophile. If electron-rich and electron-deficient alkynes are arranged in an unsymmetrical substrate, the annulation could proceed regiospecifically. We first prepared the unsymmetrically substituted diynes 1 with methoxy (1a), fluoro (1b), and trifluoromethyl substituents (1c), and attempted the gold-catalyzed reactions with them (Table 1). The annulation of methoxy-substituted diyne gave a mixture of isomers 2a and 3a in 40% yield with a ratio of 96:4 (entry 1). Fluoro-substituted diyne 1b afforded isomers 2b and 3b in 62% yield in a ratio of 42:58 (entry 2). When a trifluoromethyl group (1c), which is a strong electron-withdrawing group, was attached to the aromatic ring, the ratio of 2c and 3c was 6:94 (entry 3). Overall, the results demonstrated that the selectivity can be controlled by the electronic properties with the electron-rich alkyne acting as nucleophile, while the electron-deficient alkyne serves as the electrophile, even though the yield lower and the isomers are inseparable.

To explore another mode of substituent control of the selectivity, two o-positions of the aryl group on the alkyne were blocked by methyl groups, which probably inhibits the approach of the gold catalysts to the sterically more hindered alkyne, even though a cyclization of the vinyl cation and mesitylene followed by a 1,2-methyl shift might still be possible. The gold catalysts promoted the reaction of the diyne 1d and afforded the desired pentalene 2d in 94% yield (Table 2, entry 1). Methoxy- or trifluoromethyl-substituted diynes 1e and 1f were also converted to pentalenes 2e and 2f in 63 and 41% yield, respectively (entries 2 and 3). The annulation of bromo-substituted diyne 1g gave pentalene 2g in 60% yield, which could be useful for further transformations by common coupling reactions (entry 4). The mesityl group indeed enables a control of the pentalene synthesis. It is interesting to note that the reaction of the 2,4-dimethylbenzene-substituted diyne 1h resulted in the clean formation of the corresponding pentalene 2h in 91% yield and no generation of the pentalene 3h (entry 5). As shown in Scheme 2, the gold-catalyzed reaction of diyne 1h possibly leads to two intermediates 1a and 1b. Vinyl cation intermediate 1b might be unfavorable because the cyclization of 1b, which should proceed through a planar configuration is probably prohibited by the steric hindrance between the gold catalyst and the o-methyl substituent of the aromatic moiety. This results in the selective formation of 2h. This step could be crucial for controlling the reaction of the mesitylene-substituted diyne 1d. Overall, those results indicated that regiospecific annulation was achieved by the introduction of a mesityl group or 2,4-dimethylbenzene.

Table 1. Electronic effect on the selectivity.

| Entry | R  | Time [h] | Yield [%] | 2/3 |
|-------|----|----------|-----------|-----|
| 1     | OMe| 1        | 60        | 96:4|
| 2     | F  | 1        | 62        | 42:58|
| 3     | CF₃| 1        | 29        | 6:94|

[a] 1 (0.05 mmol), catalysts (0.005 mmol) in solvent (1 mL). [b] Combined yield of 2 and 3. [c] Determined by ¹H NMR of the crude mixture.

Table 2. Reaction of mesitylene-substituted diynes.

| Entry | Ar   | R   | Time [h] | Yield [%] |
|-------|------|-----|----------|-----------|
| 1     | mesityl | H   | 1        | 94        |
| 2     | mesityl | OMe | 3        | 63        |
| 3     | mesityl | CF₃ | 20       | 41        |
| 4     | mesityl | Br  | 20       | 60        |
| 5     | 2,4-dimethylbenzene | H | 1h       | 91        |

[a] 1 (0.05 mmol), catalysts (0.005 mmol) in solvent (2 mL). [b] Isolated yield. [c] 40 °C.
Based on the results with the diynes being blocked at the α-positions, the selective synthesis of S-shape bispentalenes should be feasible. We then designed and synthesized the benzene- and naphthalene-based tetraynes 4a and 4b with mesitylene (Scheme 3). The tetraynes 4a and 4b were conveniently prepared by sequential Sonogashira-coupling reactions of 1,4-dibromo-2,5-diiodobenzene or 3,7-dibromonaphthalene-2,6-diyl-bis(trifluoromethanesulfonate). Using (IPr)AuCl/AgNTf₂, the benzene-based tetrayne 4a was completely consumed within 2 h, the corresponding linear bispentalene 5a was obtained in 81% yield as a reddish-brown solid. In addition, the annihilation of naphthalene-based tetrayne 4b with (IPr)AuCl/AgNTf₂ proceeded at room temperature and gave the linear bispentalene 5b in 86% yield as a red solid.

The connectivity of 5b in the solid state was confirmed by X-ray crystallography (Figure 1). Due to the mesityl group, the...
previously reported n-pentyl substituted S-shape bispentalene B (Figure 2) shows significantly smaller torsion angles (34.2–37.9°) between the pentalene core and the peripheral aryl group than pentalene 5b (63.5–69.3°).

We considered tetranyne 6a, having a different substitution pattern, as another approach to access the bispentalene scaffold. It could potentially afford two isomers, 7a and 8a, because the second annulation could occur on both carbon atoms of the intermediate IIa (Scheme 4). Indeed, the intramolecular annulation with 5 mol% of gold catalysts in dichloroethane afforded pentalenes 7a and 8a in 20 and 72% yield, respectively. The structure of 8a was unambiguously confirmed by single-crystal X-ray crystallography (Figure 3). Interestingly, the pentalene core and the peripheral mesityl group are nearly vertical and the two mesityl groups are parallel.

When the cyclization of 6a was performed using (IPr)AuCl/AgNTf₂, isomers 7a and 8a were produced in a 22:78 ratio. In our previous report, the bulkiness of the ligand had a significant effect on the ratio of the resulting bispentalene isomers. Therefore, a set of different ligands on the catalysts was investigated to prove this effect on the selectivity of isomeric bispentalenes 7a and 8a.

| Entry | Catalyst                  | Time [h] | Yield [%][b] | 7a:8a Ratio | 7a:8a Ratio |
|-------|--------------------------|----------|--------------|-------------|-------------|
| 1     | (IPr)AuCl/AgNTf₂         | 2        | 20:72        | 22:78       |             |
| 2     | (IPr)Au(NCMe)SbF₆        | 1.5      | 21:72        | 23:77       |             |
| 3     | Ph₃PAuNTf₂                | 3        | 15:55        | 21:79       |             |
| 4     | NACAuCl/AgNTf₂           | 4        | ND           | ND          |             |
| 5     | (IPr)*AuCl/AgNTf₂        | 3.5      | 62[8]        | 4:96[8]     |             |
| 6     | (IPr)AuNTf₂              | 2.5      | 18:71        | 20:80       |             |
| 7     | AgNTf₂                   | 4.5      | ND           | ND          |             |
| 8     | AgNTf₂                   | 4.5      | ND           | ND          |             |
| 9     | (IPr)AuCl                | 2.5      | 18:71        | 20:80       |             |
| 10    | Ph₃PAuNTf₂               | 3.5      | 62[8]        | 4:96[8]     |             |
| 11    | NACAuCl/AgNTf₂           | 4.5      | ND           | ND          |             |

[a] Reaction performed in a vial in DCE (1 mL), 6a (0.02 mmol) and catalyst (0.005 mmol). [b] Isolated yield. [c] Combined yield of 7a and 8a. [d] Determined by ¹H NMR.

Scheme 4. Gold-catalyzed reaction to form bispentalenes 7a and 8a.
AgNTf₂ (entry 7). The short ligand screening finally revealed that the sterically bulky IPr* ligand increases the ratio of pentalen 8a (entry 5). This can be rationalized by the steric hindrance between the mesitylene substituent and the gold complex on the intermediate II, which ultimately leads to the formation of product 8a.

The selective formation of 8a was investigated by using M06-2X-CPCM/BS2//B3LYP-CPCM/BS1 calculations. It was found that the selectivity is mainly controlled by a steric repulsion between the mesitylene substituent and the IPr ligand in TS-1b (Figure 4). This destabilizing interaction is absent in TS-1a, causing this transition structure to be 0.3 kcal mol⁻¹ lower in energy than in TS-1b. To support this assertion, the IPr carbene ligand was replaced by the IMe carbene ligand, in which the bulky N-substituents of IPr are replaced by methyl groups. The results starting from this new model system are shown in Figure 5. In contrast to the real system in which TS-1a is calculated to be slightly lower in energy than TS-1b, for the less bulky model system, the energy order of the transition structures becomes reversed. In this case, TS-1b-M is calculated to be 2.0 kcal mol⁻¹ lower in energy than TS-1a-M (Figure 5). The energy order of transition structures TS-1b-M and TS-1a-M is most likely set by the thermodynamic aspects of the transformation. Indeed, 7a is about 6 kcal mol⁻¹ more stable than 8a, resulting in TS-1b-M lying lower in energy than TS-1a-M. Thus, although the formation of 7a is thermodynamically favored over 8a, the steric interaction between the IPr ligand and the Mes substituent in TS1-b leads to less 7a than 8a being formed.

Figure 4 shows quite similar energy values of TS-1a and TS-1b with TS-1a being lower in energy by 0.3 kcal mol⁻¹. This is consistent with the experimental 22:78 ratio of the two products. Figure 5 shows a higher difference in energy for TS-1a-M and TS-1b-M with a reversed order, now with TS-1b-M being lower. Since the repulsive interactions of the two aryl substituents in TS-1a and TS-1a-M are almost identical, this clearly indicates that the ligand-aryl steric interaction in TS-1b is stronger than that in TS-1b-M.

Next, several electron-withdrawing and electron-donating substituents on the aromatic moieties were investigated using [[IPr]Au(NCMe)]SbF₆ as the catalyst. In the case of tetrayne 6a, the gold-catalyzed reaction afforded bispentalenes 7a and 8a in a ratio of 22:78 (Table 4, entry 1). Fluoro-substituted substrate 6b led to the separable bispentalen isomers 7b and 8b with a ratio of 35:65 in 25 and 55% yield, respectively (entry 2). Tetrayne 6c with dimethyl substituents on the outer aromatic moieties exhibit higher selectivity towards the formation of 8c over 7c (entry 3, 91:9 ratio, 36 and 3% yield, respectively), although the overall yield significantly dropped. These results indicate that the substituents on outer aromatics influence the selectivity of the transformation.

Figure 4. The selectivity-determining step with the IPr carbene ligand (energies in kcal mol⁻¹).
The optical properties of bispentalenes 5a, 5b, 7a and 7b were examined by UV–Vis absorption spectroscopy in dichloromethane (Figure 6). Based on previous work,[4e] the two characteristic absorptions (∆λ = 450–550 nm) of 5a, 7a, and 7b might be assigned to HOMO→LUMO+1 and HOMO→LUMO transitions. The introduction of mesityl groups has a significant effect on the absorption. Thus, the absorption peaks (∆λmax = 474 and 502 nm) of mesitylene-substituted 5a were red-shifted (30 nm) compared to the S-shaped benzene-based bispentene A (∆λmax = 496 and 532 nm). A similar tendency was observed between naphthalene-based bispentalenes 5b (∆λmax = 490 and 525 nm) and B (∆λmax = 510 and 550 nm). In addition, from the comparison of 5a (∆λmax = 474 and 502 nm) and 7a (∆λmax = 460 and 490 nm), differences on the substitution position of mesityl groups caused significant blue-shift.

The HOMO and LUMO levels of the series of bispentalenes 5a, 5b, 7a, and 7b in CH2Cl2 were estimated by cyclic voltammetry (Table 5). Compared to the previously synthesized benzene-based bispentene A and naphthalene-based bispentene B (Figure 2), the HOMO levels of 5a (–5.24 eV) and 5b (–5.50 eV) are lower than the HOMO levels of the corresponding compounds A (–5.20 eV) and B (–5.38 eV). The LUMO levels of 5a (–3.11 eV) and 5b (–2.93 eV) are significantly higher than the LUMO level of the corresponding compounds A (–3.23 eV) and B (–3.09 eV), which resulted in the larger HOMO–LUMO energy gap of 5a and 5b. Based on the solid-state structure of 5b (Figure 1), the peripheral mesitylene might contribute less to the core π-system, which could have an effect on the HOMO and LUMO energy levels. The HOMO and LUMO levels of the S-shaped bispentalenes 7a (HOMO= –5.30 eV, LUMO= –3.18 eV) and 7b (HOMO= –5.40 eV, LUMO= –3.25 eV) are lower compared to 5a. The HOMO–LUMO gaps for 7a and 7b (Egap = 2.15 eV) are not significantly different from that of 5a (Egap = 2.13 eV).

Table 4. Bispentalene derivatives.[a]

| Entry | Compound | R1 | R2 | Time [h] | Yield [%][b] | 7 : 8 |
|-------|----------|----|----|---------|-------------|------|
| 1     | 6a       | H  | H  | 2       | 20:72       |      |
| 2     | 6b       | F  | H  | 2       | 25:55       |      |
| 3     | 6c       | Me | Me | 3       | 3:36        |      |

[a] Reaction performed in a vial in DCE (1 mL), 6 (0.05 mmol) and catalyst (0.005 mmol). [b] Yield of isolated product.
Table 5. Cyclic voltammetry data and estimated HOMO and LUMO energies.

| E_HOMO | E_LUMO | E_gap |
|--------|--------|-------|
| [eV]   | [eV]   | [eV]  |
| A\text{red} | 0.40 | -1.57 | -5.20 | 3.63 | 1.98 |
| 5a\text{red} | 0.44 | -1.69 | -5.24 | 3.55 | 2.13 |
| 5c | 0.58 | -1.71 | -5.38 | 3.60 | 2.29 |
| 5b | 0.70 | -1.87 | -5.50 | 3.63 | 2.57 |
| 7a | 0.51 | -1.65 | -5.30 | 3.65 | 2.15 |
| 7b | 0.60 | -1.55 | -5.40 | 3.85 | 2.15 |

[a] Cyclic voltammetry in CH_2Cl_2, containing 0.1 M nBuNPF_6 with ferrocene on a Pt working electrode, a Pt/Ti counter electrode, and an Ag reference electrode at a scan rate of 0.2 V/s. All potentials are given versus the Fc^-/Fc couple used as an internal standard. [b] Electrochemical data obtained at a scan rate of 0.2 V/s in CH_2Cl_2 containing 0.1 M nBuNPF_6 on a glassy carbon working electrode, a Pt/Ti counter electrode, and Ag reference electrode. [c] HOMO and LUMO energy levels in eV were approximated using the equation E_HOMO = -(4.80 + E_H), LUMO = -(4.80 + E_L). E_{gap} = \text{LUMO} - \text{HOMO}.

Conclusions

We report the regiospecific annulation of unsymmetrically substituted 1,2-dilaryl ethynylbenzene derivatives. Both electronic and steric effects on the aromatic moieties of the substrates are crucial for the selectivity. Especially, the introduction of electronic and steric effects on the aromatic moieties of the substrates are crucial for the selectivity. Additionally, this method provided the thermodynamically-controlled synthesis of S-shaped bispentalenes from 1,2,4,5-tetraethynylbenzene or 2,3,6,7-tetraethynaphthalene. Moreover, the annulation of a series of tetraines with a different substitution pattern regiospecifically provided bispentalenes. Our computational studies showed that 7a is the thermodynamic product of the reaction, whereas 8a is the kinetic product, preferentially formed with bulky NHC ligands (like IPr, but better IPr*).

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Conflict of interest

The authors declare no conflict of interest.

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