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Different-shaped ligand mediating efficient structurally similar cage-to-cage transformation

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ABSTRACT

The transformation of a Palladium-based metal-organic cage to a structurally similar one by direct ligand replacement usually leads to unwanted ligand scrambling. In this work, an intermediate ligand with different shape and basicity from the initial/final ones was introduced to avoid ligand scrambling to achieve the efficient indirect cage-to-similar-cage transformation. Compared with the direct transformation, the stepwise conversion has the advantages of high efficiency (93%) and simple workup.

Metal-organic cages have attracted huge attention because of their well-fined geometries and confined functional cavities, which are widely applied in drug delivery [1–4], catalysis [5–8], guest recognition [9–11] and separation [12,13], and sensing [14–17]. Ligand exchange strategies are commonly used to synthesize and tune the properties of metal-organic cages [18,19]. Palladium-based metal-organic cages with labile coordination bond can undergo ligand exchange [20] to achieve cage-to-cage transformations, which have been used to synthesize novel cages [21–25]. Compared with the direct coordination into cages, the cage-to-cage conversions, which are post-synthetic strategies originating from the ligand exchanging at the molecular level, can not only obtain higher-level self-assemblies [26–28], but also mimic the function of biosystems [29,30]. In the conversions of these Palladium-based cages, the basicity and geometric structure of the ligands are two key factors that affect the transformation efficiency. The basicity of the ligands on the initial and target cages determines the direction of transformation [31] and structural difference of ligands affects the process of cage-to-cage transformation [32]. When two ligands have large structural differences (especially the length), the initial homoleptic cage could be converted efficiently into another homoleptic cage [31,33]. When the two ligands are of complementary structure [34–36], only a single of the heteroleptic cage will be obtained, which is described as integrative self-sorting. And when the two ligands have similar structures [37,38], ligand scrambling would occur–the addition of the new ligand to the initial cage would generally lead to the formation of a series of heteroleptic cages (Fig. 1a). So far as we know, there are only a few reports of exploiting hydrogen bonding interactions and steric effects to avoid the ligand scrambling [35,39,40]. Therefore, it is of significant scientific value to develop new and universal strategies to achieve efficient interconversion of cages with similar structures.

Herein, we report the stepwise transformation of a cage (**2a**) to another one (**2b**) with similar structure in an extremely high yield by introducing an intermediate ligand (**Lm**), as illustrated in Fig. 1b. The basicity of **Lm** is between the initial cage ligand (**La**) and the target cage ligand (**Lb**), and its structure is also very different from the two. As a consequence, the intermediate cage (**2m**) can be obtained by adding **Lm** to **2a** in 96% yield, and then almost quantitatively (97%) transferred to **2b** in the presence of excess **Lb**. By comparison, the direct **2a**-to-**2b** transformation by adding **Lb** to cage **2a** leads to the formation of multiple mixed cages because of ligand scrambling, which results in a low yield (49%) of **2b** formation and makes it difficult to be purified. This mediated cage-to-cage transformation provides a universal strategy for effective preparation of molecular cages from their counterparts with weaker ligand basicity.

The structures of **La**, **Lm** and **Lb** are shown in Fig. 2. Both **La** and **Lb** are V-shaped ligands while **Lm** adopts a quite different configuration with an azobenzene connecting with two *meta*-

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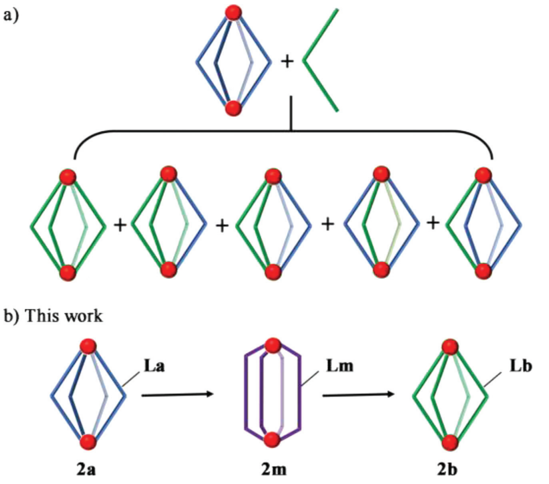

Fig. 1. Cartoon illustration of (a) cage-to-cage transformation with similar structure; (b) step-by-step transformation of cage **2a** to **2b** by introduction of a mediated ligand **Lm**.

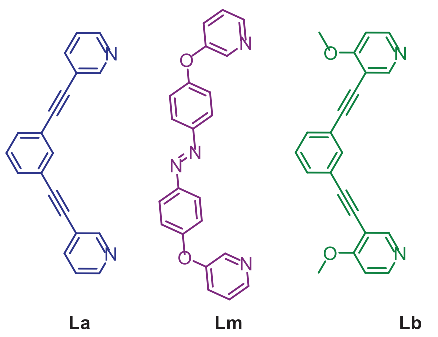

Fig. 2. Structures of the ligands used in this study.

pyridines. The introduction of phenyloxy weak electron donating group on the *meta* position of **Lm**-pyridine was expected to make the basicity of **Lm** weaker than **Lb** (methoxy strong electron donating groups stay on the *para* position of **Lb**-pyridine) but stronger than **La** (no electron donating group on the **La**-pyridine).

La [41] and **Lb** [31] were prepared as reported and **Lm** was synthesized by the reduction of 3-(4-nitrophenoxy)pyridine (Scheme S1 in Supporting information). The relative basicity investment was carried out by ^{1}H NMR trifluoroacetic acid titration experiments. **Lm** was found to be protonated more easily than **La** (Figs. S4 and S5 in Supporting information), and **Lb** was protonated more readily when compared to **Lm** (Figs. S6 and S7 in Supporting information). The basicity sequence **La** < **Lm** < **Lb** was thus confirmed.

The known **2a** [41] and **2b** [31] were then synthesized by the self-assembling of **La** and **Lb** with $[Pd(CH_3CN)_4](BF_4)_2$ respectively. The mediated cage **2m** was obtained similarly by stirring **Lm** and $[Pd(CH_3CN)_4](BF_4)_2$ in 2:1 ratio in CD_3CN at 70 °C for 5 h. **2m** was characterized by ^{1}H, ^{13}C, DOSY and ^{1}H–^{1}H COSY NMR spectroscopy and high-resolution mass spectrometry. Further X-ray single crystal analysis reveals that **2m** crystallizes in monoclinic crystal system with C 2/c space group, and each square-planar Pd^{2+} is coordinated to four N atoms on pyridine of different **Lm**, generating the lantern shaped M_2L_4 structure (Fig. S13 and Table S1 in Supporting information) [42–44], which is the same pattern as **2a** and **2b**.

The direct cage-to-cage conversion was subsequently carried out by mixing **2a** with **Lb** in different molar ratios (1.0: 2.0, 4.0, 7.0) in CD_3CN at room temperature for 24 h (Scheme S4 in Supporting information). The ^{1}H NMR results (Fig. S14 in Supporting information) indicate that **2a** disappears while **2b** comes into being after the addition of **Lb**. Except for those proton signals of **2b** and the released free **La** and **Lb**, the rest peaks are difficult to be clearly assigned. Nevertheless, further high-resolution mass spectrometry (Fig. 3) shows that the reaction mixture also contains hybrid molecular cages, such as $[Pd_2(\mathbf{La})(\mathbf{Lb})_3](BF_4)_4$ (abbreviate as **H1**, *m/z* at 378.5711 for $[\mathbf{H1}–4BF_4]^{4+}$, 533.7686 for $[\mathbf{H1}–3BF_4]^{3+}$, 844.1517 for $[\mathbf{H1}–2BF_4]^{2+}$) and $[Pd_2(\mathbf{La})_2(\mathbf{Lb})_2](BF_4)_4$ (abbreviate as **H2**, *m/z* 363.5635 for $[\mathbf{H2}–4BF_4]^{4+}$, 513.7659 for $[\mathbf{H2}–3BF_4]^{3+}$, 814.1346 for $[\mathbf{H2}–2BF_4]^{2+}$). These results indicate that obvious ligand scrambling occurs even though the basicity of **Lb** is stronger than that of **La**. Even though 7 equiv. **Lb** was used, the conversion efficiency was determined as low as 49% according to the NMR integrations (Figs. S15 and S16 in Supporting information). It should be noted that we failed to obtain pure **2b** after several purification attempts, such as recrystallization and washing with poor solvents.

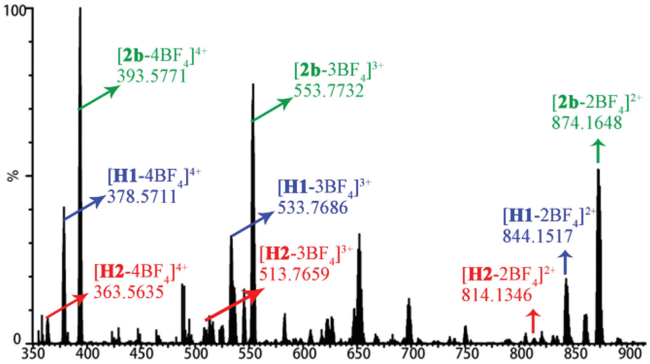

Fig. 3. ESI-MS spectrum of reaction mixture of direct transformation from **2a** to **2b** by mixing **2a** and **Lb** in a 1.0: 7.0 molar ratio in CH_3CN at room temperature.

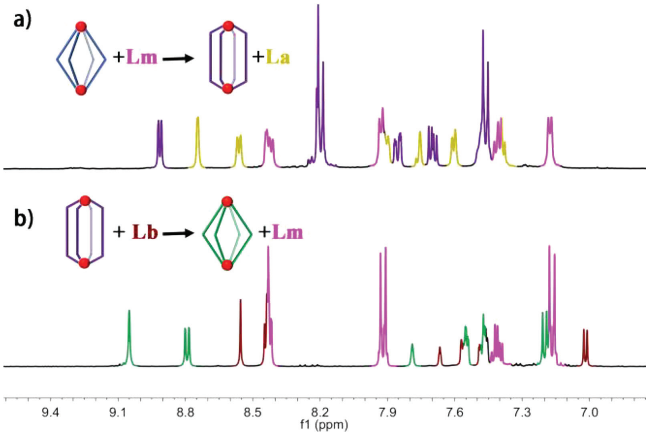

Fig. 4. ^{1}H NMR spectra (400 MHz, CD_3CN) of mixtures after stirring at room temperature for 24 h of (a) **2a** and **Lm** in a 1.0: 7.0 molar ratio, (b) **2m** and **Lb** in a 1.0: 7.0 molar ratio.

The step-by-step conversions from cage **2a** to **2m** and then to **2b** (Scheme S3 in Supporting information) were then conducted. The first cage conversion process was investigated by treating **2a** with **Lm** at room temperature for 24 h in CD_3CN (Scheme S5 in Supporting information). As shown in Fig. S17 (Supporting information), a new set of ^{1}H NMR peaks corresponding to **2m** appears with the addition of 2.0 equiv. of **Lm**, and its intensity increases with the further addition of **Lm**, while the peaks of **2a** gradually disappear. The ^{1}H NMR results suggest that **2a** was completely transferred into **2m** after the addition of 7.0 equiv. of **Lm** (Fig. 4a). This conversion process was further confirmed by ESI-MS spectrometry of the mixtures of **2a** and **Lm**. Both **2a** and **2m** peaks occur when the molar ratio of **Lm** to **2a** is 2.0 (Fig. S19 in Supporting information), while those **2a** ones disappear when the ratio come to 7.0 (Fig. S20 in Supporting information). The additional free **La** and **Lm** were removed by the simply addition of ethyl ether to the clear solution and **2m** precipitated out. Further preparative experiment was conducted in CH_3CN, and pure **2m** was obtained from ethyl ether in a high yield of 96% (Scheme S5 in Supporting information).

The transformation of cage **2m** to **2b** was finally carried out. Similarly, the ^1H NMR spectra were recorded after the progressive addition of **Lb** (2.0, 4.0 and 7.0 equiv.) to the CD_3CN solution of **2m** at room temperature for 24 h (Scheme S6 and Fig. S21 in Supporting information). It can be found that the proton signals of **2b** enhance with the addition of **Lb**, and those of **2m** disappear entirely when the molar ratio of **Lb** to **2m** reaches to 7.0 (Fig. 4b). Pure **2b** was obtained after being precipitated from ethyl acetate in 97% yield in the preparative experiment (Scheme S6).

Further experiments of the mixing of cage **2b** with different amounts of **Lm** (2.0, 4.0 and 7.0 equiv.) were conducted to investigate the details of the back-transformation of **2b** to **2m**. According to the integrations of ^1H NMR spectrometry, the conversions are 7%, 12% and 19% respectively with the increasing addition of **Lm** (Fig. S23 in Supporting information) and the peaks of **2m**, **2b**, **Lm** and **Lb** all appear in the ESI-MS of the mixture of **2b** with 2.0 and 7.0 equiv. of **Lm** (Figs. S24 and S25 in Supporting information). These results indicate that the cage-to-cage conversion is a dynamic equilibrium process.

It can be seen that both direct and stepwise cage-to-cage transformations can be performed at room temperature. Compared with the low efficiency (49%) of the former, the latter has one more reaction step, but the yield has been greatly improved to 93% (*i.e.*, $96\% \times 97\%$) after simple work-up. In addition, this cage transformation method of introducing a mediated ligand with large structural differences can well solve the problem of ligand scrambling without requiring additional modifications to the initial and final cages.

In summary, the direct conversion of cage **2a** to **2b** results in the formation of heteroleptic cages because of serious ligand scrambling between **La** and **Lb**, making the conversion process complex. To avoid this ligand scrambling, an intermediate ligand **Lm** with different shape and basicity from **La**/ **Lb** was introduced and **2a** was indirectly converted to **2b** *via* the intermediate cage **2m**. The latter mediated method possesses the advantage of high yield and simple operation, providing a new idea for preparing molecular cages from those ones with similar structure. This research further supports that the geometry and basicity of ligand are key factors among the cage-to-cage transformation. And furthermore, such a strategy of achieving effective cage-to-cage transformation in a controlled manner has good potential application prospects in the constructions of molecular machines and drug delivery systems.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.07.036.

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