Expedient Synthesis of *E*-Hydrazone Esters and 1*H*-Indazole Scaffolds through Heterogeneous Single-Atom Platinum Catalysis

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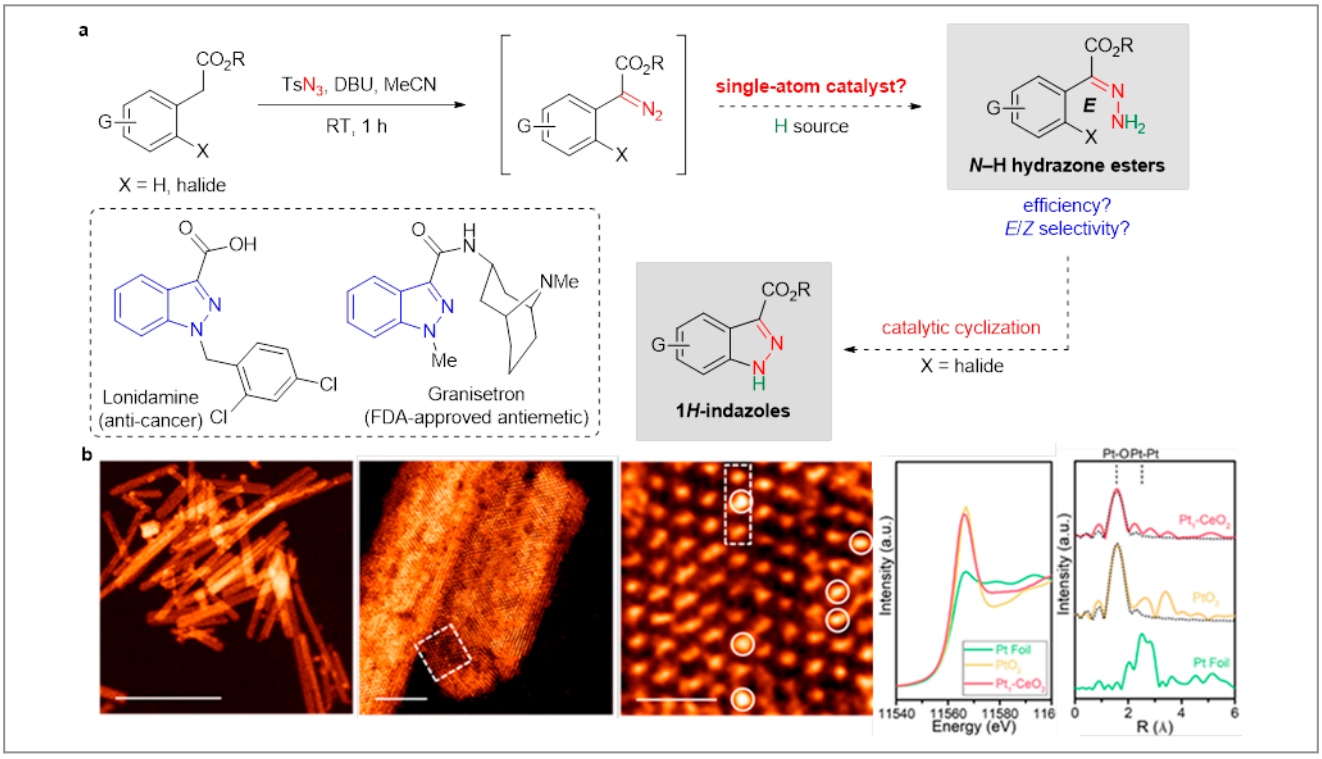
Single-atom catalysts (SACs) with the distinct advantage of ultra-high performance-to-metal ratios have been actively explored on many energy-related frontiers.[1–3] "Despite their superior performance in gas-phase reactions, SACs are typically ineffective and rarely utilized to construct medicinally important structures under liquid-phase conditions," said Professor Kian Ping Loh from the National University of Singapore. "One such class of medicinally relevant molecules is that of the 1*H*-indazole compounds." Professor Ming Joo Koh, an expert in organic synthesis from the same school, remarked: "However, access to 1*H*-indazoles requires the synthesis of stereodefined and unprotected *E*-α-hydrazone esters, which is often difficult to achieve by conventional strategies." Both Professor Loh and Professor Koh then wondered whether it would have been possible to identify a stable SAC system that is capable of promoting stereoselective generation of *N*-H hydrazone esters en route to 1*H*-indazoles.

Recently, the groups of Professor Loh and Professor Koh demonstrated that Pt single atoms anchored on defect-rich CeO_2 nanorods (Pt_1/CeO_2) promote exceptionally *E*-selective hydrogenation of α-diazoesters to afford a wide assortment of *E*-α-hydrazone esters by the catalytic alcoholysis of ammonia borane ($NH_3{\cdot}BH_3$) (Scheme 1a).



Scheme 1 The significance and challenges in developing heterogeneous single-atom metal catalysts that furnish *E*-hydrazones and 1*H*-indazoles. (a) 1*H*-Indazoles are common entities in medicinally relevant compounds and are conventionally derived from unprotected *E*-hydrazone precursors, the synthesis of which is non-trivial. An attractive approach to *E*-hydrazones involved *in situ* diazo formation followed by catalytic hydrogenation in one sequence. (b) STEM-HAADF images; atomic-resolution STEM-HAADF images of Pt_1/CeO_2 nanorods; Pt L_3-edge XANES; EXAFS spectra of Pt foil, PtO_2, Pt_1/CeO_2 nanorods; dashed lines represent the simulated EXAFS spectra.

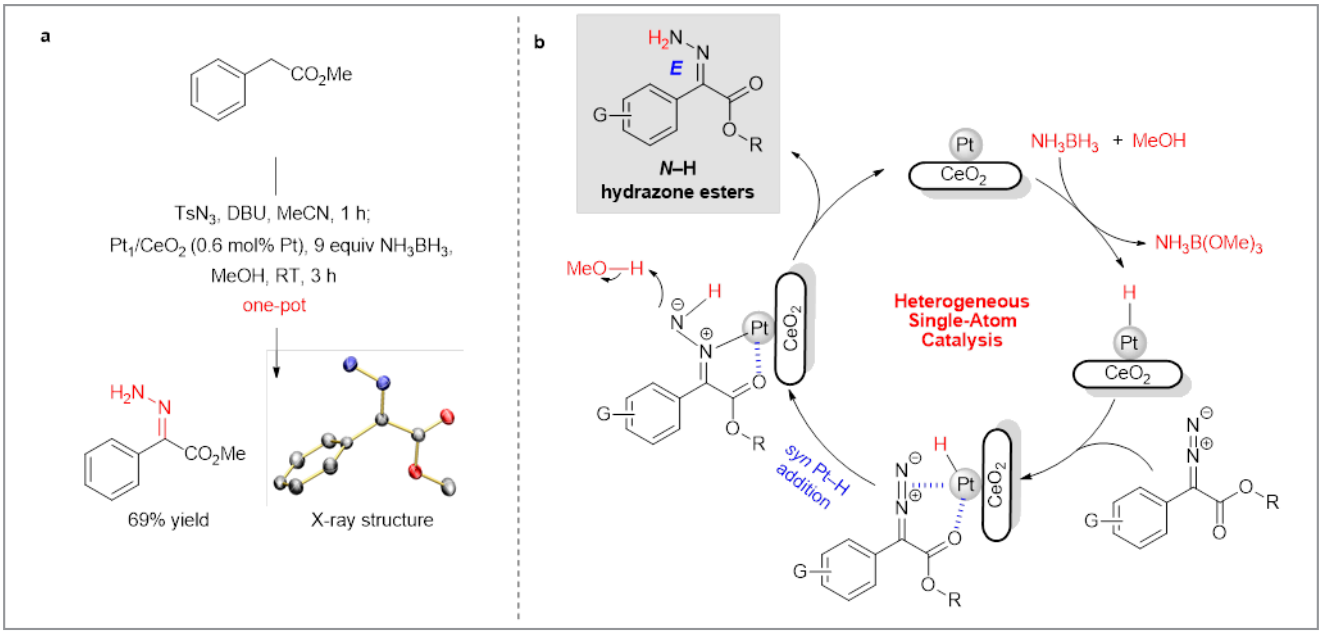
"The support is the key for developing a highly stable SAC. Defective CeO_2 with paired Ce^{3+}/Ce^{4+} redox couple and rich oxygen vacancies is the ideal candidate for anchoring and stabilizing metal single atoms," said Dr. Cuibo Liu, the first author of this paper. He continued: "The Pt_1/CeO_2 catalysts were prepared by atomic layer deposition (ALD). The atomic feature of Pt SAC can be observed through scanning transmission electron microscopy." Dr. Zhongxin Chen, the article's co-first author, added: "By using X-ray absorption spectroscopy, we could confirm the Pt configuration in the catalyst, which has a coordination number of 4 and prominent Pt–O bonding (Scheme 1b)."

By using Pt_1/CeO_2 as catalyst and $NH_3{\cdot}BH_3$ as a hydrogen source, a wide range of functionalized α-diazoesters were selectively hydrogenated to unprotected *E*-α-hydrazone esters with good efficiency. "Defective CeO_2 nanorods with atomically dispersed Pt single atoms favor the activation of substrates on surface and deliver the products in better yields and selectivity than conventional homogeneous synthetic methods," said Professor Loh. "Other reducible functional groups are tolerated under the mild reaction conditions and the catalyst is stable owing to the unique features of the CeO_2 support."

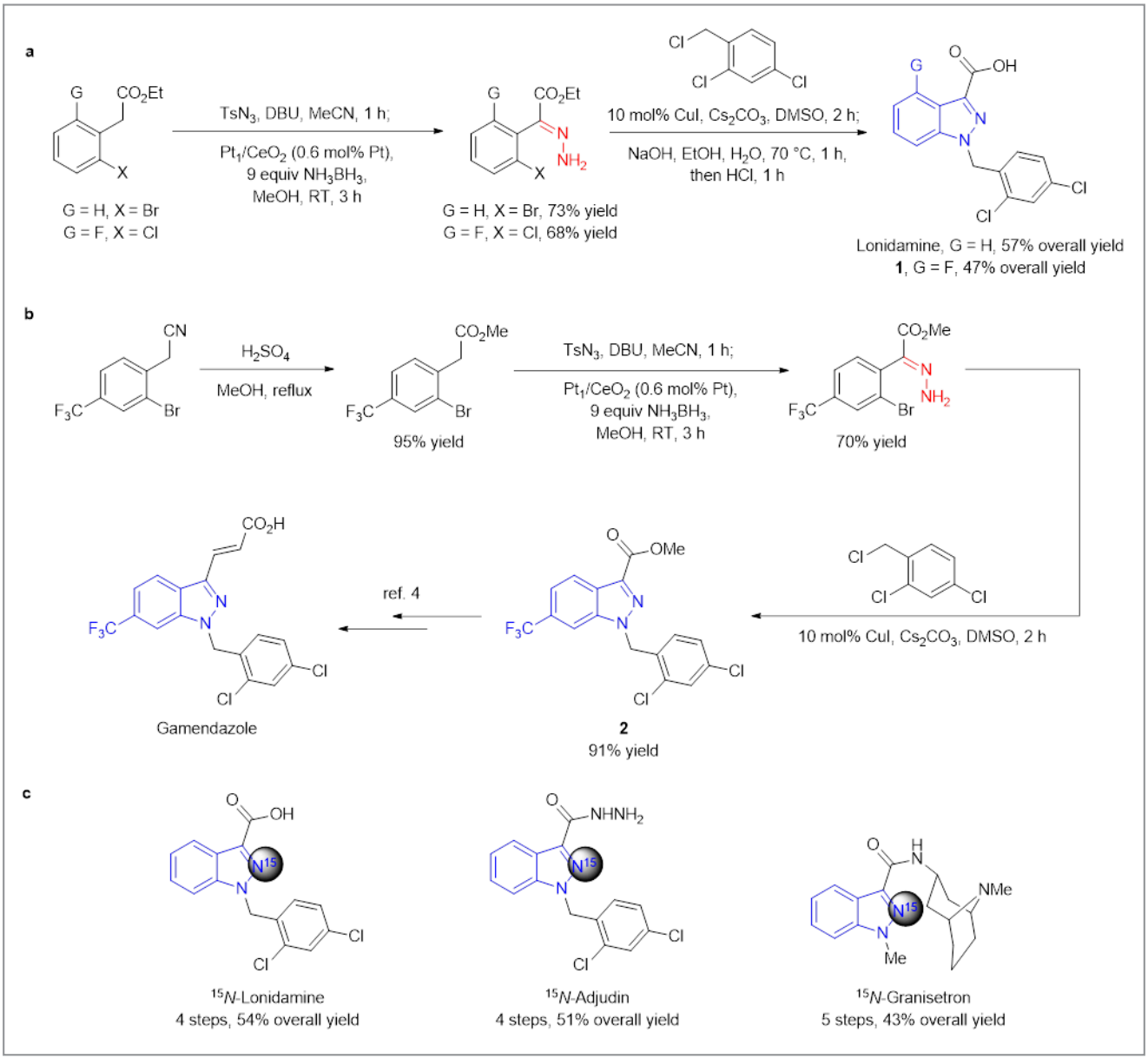
The direct synthesis of unprotected α-hydrazone esters in *E* configuration is a remarkable feature of this research work, which was very challenging to accomplish given that the *Z* isomers are thermodynamically favored over the *E* isomers. Professor Loh explained: "Simultaneous coordination of a Pt site with the diazo N=N and ester carbonyl motifs plays a central role in controlling the selectivity." The DFT calculations were used to verify the coordination effect of Pt sites and the favorable *E* configuration (Scheme 2).

Professor Koh further remarked: "The diazo substrates can be generated in situ from readily available carboxylic esters in one-pot for subsequent hydrogenation to *E*-α-hydrazone esters, by-passing the tedious purification of diazo precursors. We have realized the gram-scale synthesis of *E*-α-hydrazone esters for preparing 1*H*-indazole related pharmaceuticals and their ^{15}N-labeled derivatives" (Scheme 3).

Professor Loh concluded by examining future perspectives of this work: "By developing the highly efficient and robust Pt_1/CeO_2 SAC, we have not just provided a new platform for the expedient synthesis of *E*-α-hydrazone esters and 1*H*-indazole scaffolds. This work also serves to highlight that heterogeneous SACs can be successfully implemented in liquid-phase systems, which are typically dominated by homogeneous reactions, to facilitate the assembly of complex molecules. Further exploration of synthetic methods for scalable fabrication of SACs towards the rapid generation of molecular complexity has become more promising than ever."



Scheme 2 *E*-Selective synthesis of *N*-H hydrazone esters. (a) Direct conversion of readily available carboxylic esters into *N*-H *E*-hydrazones in a single vessel enhances the practicality of our catalytic method. (b) Proposed catalytic cycle highlighting the importance of the ester moiety in directing regio- and stereoselective Pt–H addition across the diazo N=N bond.



Scheme 3 Synthesis of 1*H*-indazole-derived biologically active compounds. (a) Anti-cancer lonidamine was assembled in 42% overall yield by a concise two-pot sequence, which may be used to prepare derivatives such as **1**. (b) Formal synthesis of gamendazole, a drug candidate for male contraception, was accomplished in 61% overall yield within 3 steps through 1*H*-indazole intermediate **2**. (c) The versatility of our protocol is further highlighted through facile preparation of ^{15}N-labelled analogues of key therapeutic agents.

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