

Project Title:**Density functional theory studies on the mechanisms of transition metal mediated chemical transformations****Name:**

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1. Background and purpose of the project, relationship of the project with other projects

Benzo-fused carbocycles such as indanes and tetralins, especially those bearing an all-carbon quaternary stereocenter, are important structural motifs in a broad spectrum of natural products, bioactive molecules and functional materials. Therefore, the development of efficient and selective methods for the synthesis of indane and tetralin derivatives having an all-carbon quaternary stereocenter is of much interest and importance. In principle, the Markovnikov-selective intramolecular C-H addition of an aromatic unit to 1,1-disubstituted alkenes would be the most atom-economical and straightforward route for the construction of indane and tetralin skeletons bearing an all-carbon quaternary center. However, this approach has met with only limited success to date because of the lack of suitable catalysts.

Recently, half-sandwich rare-earth catalysts have been found that could serve as a unique platform for various chemical transformations, including C-H alkylation with alkenes. In the course of these studies, we became interested in exploring the potential of rare-earth catalysts for the construction of important carbocycles through intramolecular C-H alkylation with alkenes. Herein, we report for the first time the annulation of a wide range of functionalized aromatic

substrates with 1,1-disubstituted alkenes via rare-earth-catalyzed regioselective C(sp²)-H and benzylic C(sp³)-H activation (**Fig. 1**). The reaction took place in an *exo*-selective fashion, constituting an efficient and selective route for the synthesis of a new family of indane and tetralin derivatives with an all-carbon quaternary stereocenter which were difficult to access previously. To have a better understand the mechanism and *exo*-selectivity of this reaction, DFT calculations were performed.

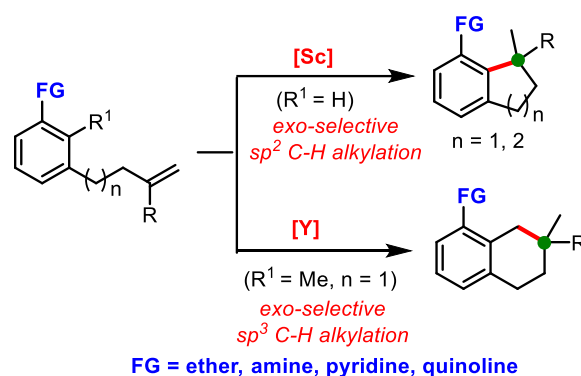


Fig. 1. Rare-earth-catalyzed *exo*-selective annulation affording an all-carbon quaternary stereocenter.

2. Specific usage status of the system and calculation method

In the last FY2022, 40% computing resources were used for my Quick User project. All calculations were performed by Gaussian 16 software together with DFT methods, such as B3LYP, B3LYP-D3, M06, M06L, M062X, B3PW91 and so on.

3. Result

As shown in Fig. 2, the coordination of the methoxy group of **1t** to the Sc atom in the cationic species $[(C_5Me_5)Sc(CH_2C_6H_4NMe_2-o)]^+$ (**cat-Sc**) generated by the reaction of **Sc-2** with $[Ph_3C][B(C_6F_5)_4]^{[10]}$ gave a more stable intermediate **A_o**, which after C-H activation at the C2 position of the coordinated anisole unit through σ -bond metathesis with the benzyl scandium species yielded the anisyl species **A**. This process required overcoming an energy barrier of 24.4 kcal/mol. Replacement of the σ -Me₂NC₆H₄Me ligand in **A** with another molecule of **1t** could afford

B, which may subsequently be transformed to **C** through the intramolecular coordination of the C=C bond in the anisyl group to the metal center. The insertion of the coordinated C=C bond into the anisyl Sc-C bond (cyclization) in **C** could easily occur in an *exo*-selective fashion by overcoming an energy barrier of 13.2 kcal/mol via transition state **exo-TS2**, thus forming a five-membered ring with a quaternary stereocenter (**D**). In comparison, the *endo*-selective C=C insertion in **C** via **endo-TS2** to give a six-membered ring product **D'** would require a much higher activation energy (38.0 kcal/mol).

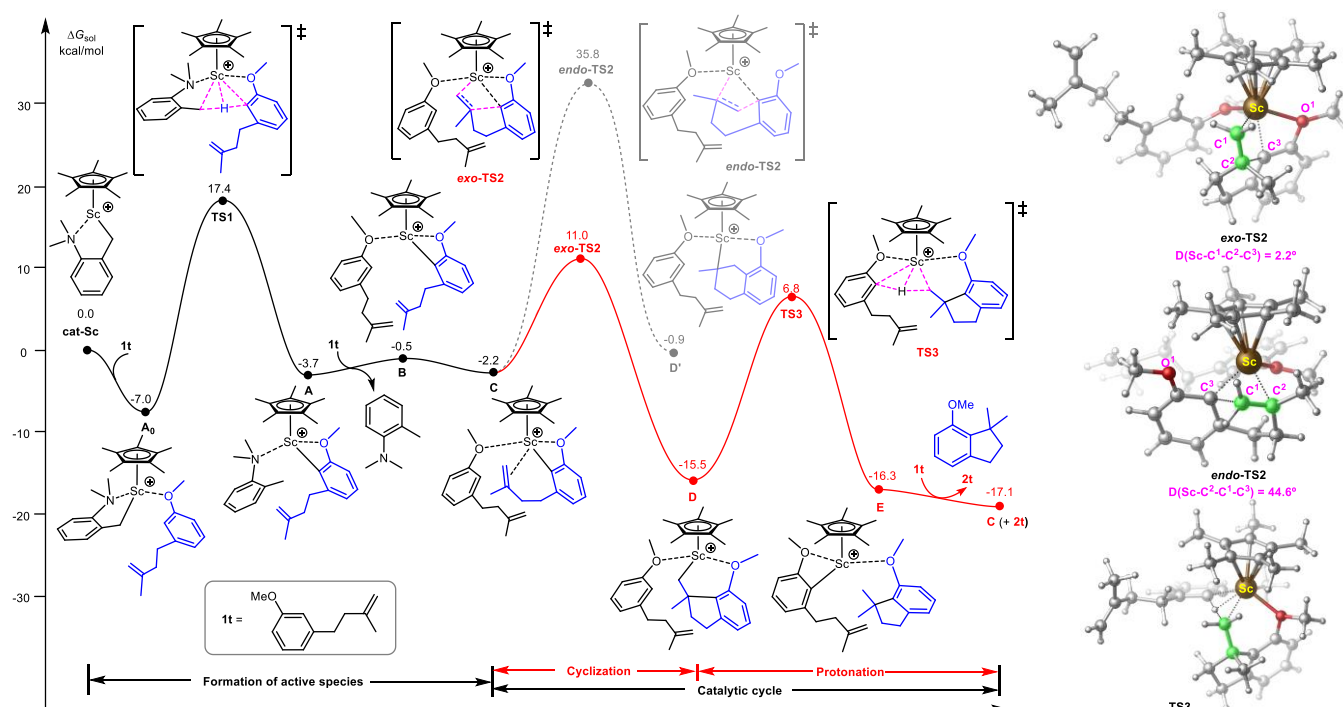


Fig. 2. Energy profile for the scenarios of the intramolecular C-H annulation of an alkenyl-substituted anisole (**1t**) catalyzed by **Sc-2**. The relative free energies (ΔG^\ddagger , kcal/mol) in solution were calculated at the level of M06/6-311+G(d,p)&SDD (SMD, toluene)//B3PW91/6-31G(d)&SDD.

The large difference in activation energy between **exo-TS2** and **endo-TS2** was caused by both steric and electronic factors. In **endo-TS2**, there was a large distortion in the core four-membered ring (Sc-C2-C1-C3) as shown by the large distorted dihedral angle $D(Sc-C2-C1-C3) = 44.6^\circ$, and the coordination interaction between the Sc atom and the O1 atom in the anisyl unit no longer existed. However, in **exo-TS2** the four-membered ring (Sc-C1-C2-C3) was almost planar ($D(Sc-C1-C2-C3) = 2.2^\circ$) without

showing a significant distortion.^[18] The C2-H activation of the coordinated anisole unit by the Sc-C alkyl bond in **D** could yield **E**, which upon coordination of another molecule of **1t** finally released the *exo*-annulation product **2t** and regenerated the catalytic species **C**. The transformation of **D** to **E** via transition state **TS3** ($\Delta G^\ddagger = 22.3$ kcal/mol) represents the rate-determining step in the catalytic cycle, in agreement with the KIE observed experimentally.

4. Conclusion

On the basis of DFT calculations, a possible reaction mechanism for the *exo*-selective annulation was revealed (**Fig. 3**). The coordination of the anisole unit of **1t** to the Sc atom in the cationic species **cat-Sc** would give an adduct complex like **A_o**, which may undergo either C2-H activation through *s*-bond metathesis to afford the corresponding anisyl species **A**. The replacement of the *o*-Me₂NC₆H₄Me ligand in **A** with another molecule of **1t** through ether coordination to the metal center could afford **B**, which may subsequently be transformed to **C**. The *exo*-selective intramolecular insertion of the coordinated C=C bond into the anisyl Sc–C bond in **C** would afford an indane skeleton with an all-carbon quaternary stereocenter like **D**. The C2-H activation of the coordinated anisole unit by the Sc–C alkyl bond in **D** may give **E**, which upon coordination of another molecule of **1t** would finally release the indane product **2t** and regenerate the catalytic species **C**.

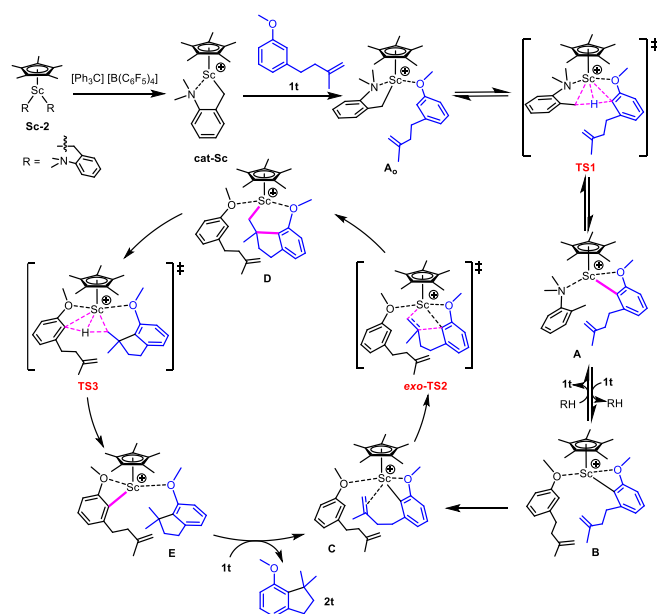


Fig. 3. Possible reaction mechanism for *exo*-selective annulation of **1t** by **Sc-2** on the basis of DFT calculations.

5. Schedule and prospect for the future

In the following FY2023, I plan to continue collaboration with Prof. Zhaomin Hou (Organometallic Chemistry Laboratory & Advanced Catalysis Research Group, RIKEN) to investigate the

related mechanisms of the metal-mediated homogeneous chemical reactions, including small molecule activation, olefin polymerization, C–H alkylation and so on. The mechanism will also be investigated by DFT calculations. Therefore, I want to get the continuous support from RIKEN Supercomputer System in the future.

Usage Report for Fiscal Year 2022

Fiscal Year 2022 List of Publications Resulting from the Use of the supercomputer

1. Aniket Mishra, Ping Wu, Xuefeng Cong, Masayoshi Nishiura, **Gen Luo***, Zhaomin Hou*. Exo-Selective Intramolecular C–H Alkylation with 1,1-Disubstituted Alkenes by Rare-Earth Catalysts: Construction of Indanes and Tetralins with an All-Carbon Quaternary Center. *ACS Catalysis* **2022**, *12*, 12973–12983. (Publication Date: Oct. 11th, 2022; Impact Factor: 13.700)