Usage Report for Fiscal Year 2024

Project Title:

Theoretical simulation on transition-metal mediated chemical transformations

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

Transition-metal mediated chemical transformations have garnered significant attention over the past few decades due to their crucial role in organic synthesis and organometallic chemistry. Prof. Zhaomin Hou's group (Organometallic Chemistry Laboratory & Advanced Catalysis Research Group, RIKEN) has made numerous groundbreaking contributions to this field over the last two decades. As is well known, a thorough understanding of the precise reaction mechanisms is essential in chemistry, as it aids in improving reaction activity and selectivity, as well as in the design of more efficient complexes and novel reactions. However, isolating and detecting intermediates during many chemical reactions remains experimentally challenging. Density functional theory (DFT) calculations, as a powerful tool, play a pivotal role in elucidating chemical reaction mechanisms. Over the past decade, in collaboration with Prof. Hou's group, I have contributed to several mechanism investigations of homogeneous reactions, significantly advancing the development of catalytic processes (e.g., *Science*, **2013**, *340*, 1549; *JACS* **2016**, *138*, 11550, *Nat. Commun.* **2017**, *8*, 1866; *JACS*, **2017**, *139*, 1818; *JACS* **2019**, *141,* 2713; *JACS* **2020**, *142*, 18128, *JACS* **2021**, *143,* 20462, *JACS* **2021**, *143*, 2470). Prof. Hou and his team continue to explore new reactions experimentally, and a deeper molecular-level understanding of these reactions is urgently needed. Clearly, DFT calculations offer an effective approach to uncovering detailed mechanisms, which can further the development of new catalysts and reactions. In FY2024, with the support of RIKEN's supercomputer system, we published several important results in high-impact journals (*ACIE* 2025, 137, e202419567; *Nature* **2024**, *632*, 307.)

2. Specific usage status of the system and calculation method

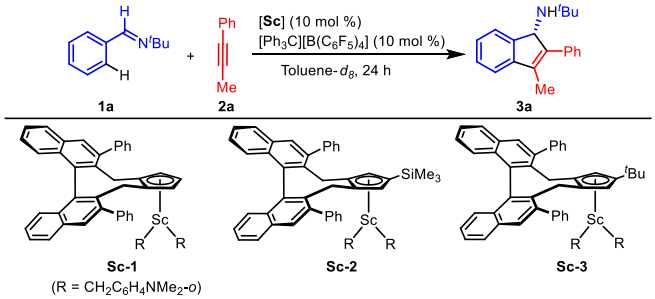
In the last FY2024, 60% computing resources were used for my User project. All calculations were performed by Gaussian 16 software together with DFT methods, such as B3LYP, B3LYP-D3, M06, M06L, M062X, B3PW91 and so on.

3. Result

(1) Scandium-Catalyzed Enantioselective [3+2] Annulation of Aldimines with Alkynes

Chiral 1-aminoindenes are important components in a wide array of natural products, bioactive molecules, and functional materials. Therefore, developing selective and efficient methods for the synthesis of chiral 1-aminoindene derivatives is of significant importance. In principle, the asymmetric [3+2] annulation of readily accessible aldimines with internal alkynes via C–H activation could serve as an atom-efficient and straightforward route for synthesizing densely functionalized chiral 1-aminoindenes bearing a stereodefined amino functional group. However, despite extensive studies and recent advances in various C–H activation-involved annulation reactions, the enantioselective [3+2] annulation of aldimines with alkynes via C–H activation has remained a challenge to date. Recently, we report

the first enantioselective [3+2] annulation of aldimines with a wide range of internal alkynes via C–H activation using chiral half-sandwich scandium catalysts (Figure 1).



Entry	[Sc]	T (°C)	Yield (%)[b]	e.r.[c]
1	**Sc-1**	80	22	31:69
2	**Sc-2**	80	90	88:12
3	**Sc-3**	80	84	96:4
4	**Sc-3**	**70**	**84**	**97:3**
5	**Sc-3**	60	73	97:3

Figure 1. Asymmetric [3+2] annulation of aldimine **1a** with alkyne **2a** by half-sandwich scandium catalysts with varying cyclopentadienyl ligands.

To elucidate the reaction mechanism, DFT calculations on the reaction of *N*-*tert*-butylbenzaldimine (**1a**) with 1-phenyl-1-propyne (**2a**) using **Sc-3** were performed (Figure 2). The coordination of the imine group of **1a** to the Sc atom in the cationic species $[(C_p^{chiral})Sc(CH_2C_6H_4NMe_2\text{-}o)]^+$ (**A**), generated by the reaction of **Sc-3** with $[Ph_3C][B(C_6F_5)_4]$,[13] could yield a more stable intermediate **B**, which after C(sp^2)–H activation at the C2 position of the phenyl unit in the coordinated **1a** through transition state **TS1** gives the intermediate species **C**, which bears *o*-$Me_2NC_6H_4Me$ as a neutral coordination ligand. This process overcomes an energy barrier of 23.5 kcal/mol. The release of *o*-$Me_2NC_6H_4Me$ from **C** may afford a more stable species **D**. The subsequent alkyne insertion into the Sc–C bond in **D** could occur selectively via transition state (*S*)-**TS2** ($\Delta G^{\ddagger}$ = 18.7 kcal/mol), leading to the formation of (*S*)-**E**. Notably, the enantiomeric transition state (*R*)-**TS2** ($\Delta G^{\ddagger}$ = 21.1 kcal/mol) and the regioisomeric transition state (*S*)-**TS2'** ($\Delta G^{\ddagger}$ = 20.7 kcal/mol) exhibit higher energy barriers than (*S*)-**TS2** by 2.4 and 2.0 kcal/mol, respectively. The intramolecular nucleophilic addition (cyclization) of the Sc-alkenyl bond to the C=N unit in (*S*)-**E** would easily take place *via* transition state (*S*)-**TS3** ($\Delta G^{\ddagger}$ = 7.5 kcal/mol), producing the Sc amido species (*S*)-**F**. The coordination of another molecule of **1a** to the Sc atom in (*S*)-**F**, followed by the acid-base reaction between the Sc-amido bond and a phenyl *ortho*-C(sp^2)–H bond of the coordinated **1a** *via* (*S*)-**TS4** ($\Delta G^{\ddagger}$ = 22.0 kcal/mol), ultimately affords the asymmetric [3+2] annulation product (*S*)-**3a** and regenerates the catalytically active species **D**.

To understand why **Sc-3** with a *tert*-Bu-substituted Cp ligand exhibited higher enantioselectivity than the Me_3Si-substituted analog **Sc-2** (Table 1, entries 2 and 3), the two enantiomeric transition states (*S*)-**TS2** and (*R*)-**TS2** were further analyzed. It was found that there was a C–H···π noncovalent interaction between the *tert*-butyl group on the Cp ring and the phenyl unit of the benzaldimine unit in (*S*)-**TS2**, but such noncovalent interaction was absent in (*R*)-**TS2** (Figure 3a and 3b). Moreover, there was a steric repulsion between the *tert*-butyl group on the Cp ring and the *N*-*tert*-butyl unit in the benzaldimine moiety in (*R*)-**TS2**, as shown by the short distance between H^1 and H^2 (d = 2.10 Å). In the case of **Sc-2** with the $SiMe_3$ substituent (Figure 3c), the energy difference between the favored transition state (*S*)-**TS2** and disfavored (*R*)-**TS2** ($\Delta\Delta G^{\ddagger}$ = 1.2 kcal/mol) was smaller than that in the case of **Sc-3** ($\Delta\Delta G^{\ddagger}$ = 2.4 kcal/mol). The C–H···π interaction between a methyl group in $SiMe_3$ and the phenyl unit of the benzaldimine unit in (*S*)-**TS2**$_{(Sc\text{-}2)}$ was weaker than that between a methyl group in ^{t}Bu and the phenyl unit of the benzaldimine unit in (*S*)-**TS2**$_{(Sc\text{-}3)}$ ($d_{H\cdots Ph}$ = 2.93 for **Sc-2** *vs* 2.66 Å for **Sc-3**). This difference could also

be visualized intuitively by the noncovalent

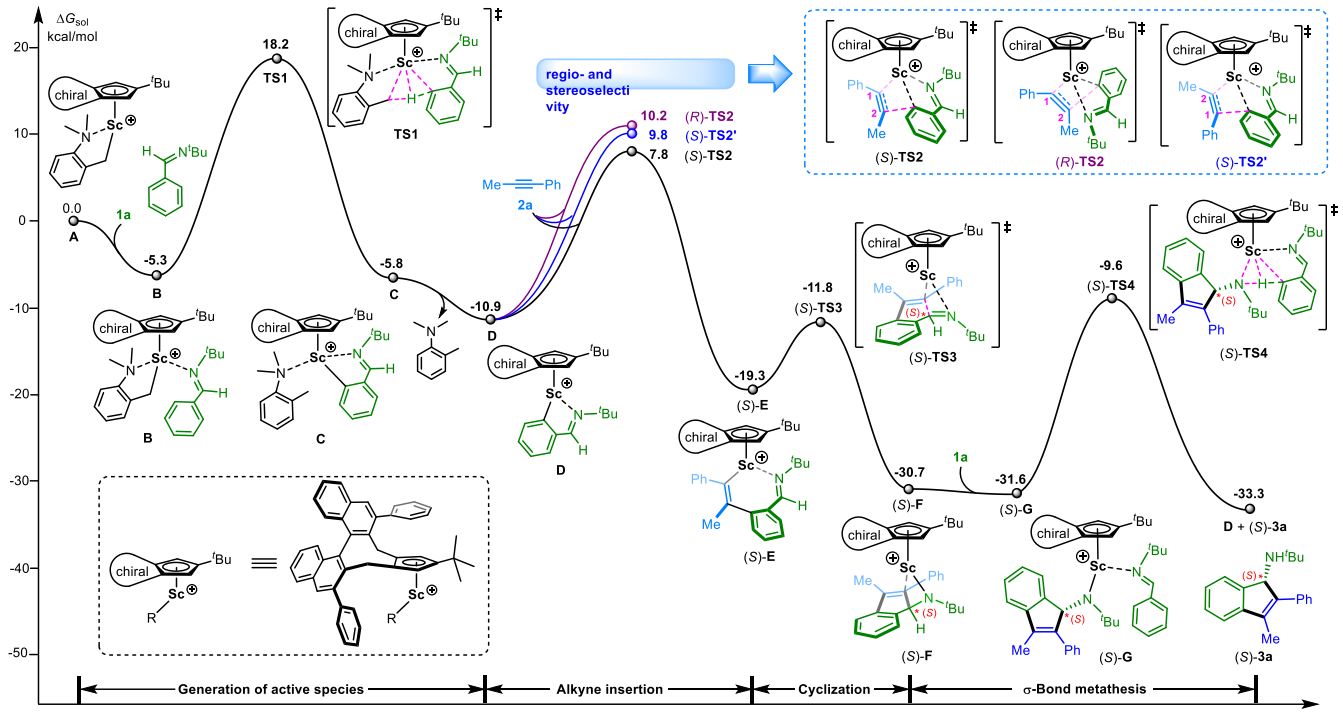


Figure 2. Computed energy profile (kcal/mol) of the asymmetric [3+2] annulation of **1a** with **2a** by **Sc-3**.

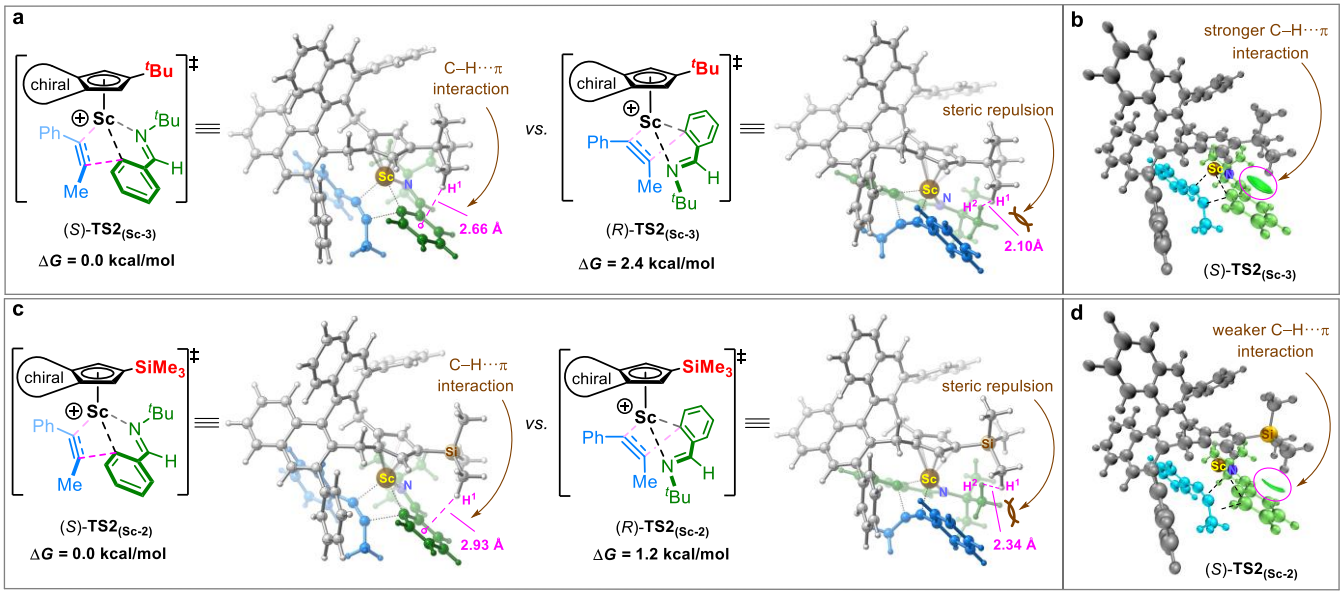


Figure 3. (a) Computational analysis of the origin of enantioselectivity of rare-earth catalyst **Sc-3**. (b) Noncovalent interaction (NCI) analysis of the C–H···π interaction in (*S*)-**TS2**$_{(Sc\text{-}3)}$ (Isovalue = 0.005). (c) Computational analysis of the origin of enantioselectivity of rare-earth catalyst **Sc-2**. (d) Noncovalent interaction (NCI) analysis of the C–H···π interaction in (*S*)-**TS2**$_{(Sc\text{-}2)}$ (Isovalue = 0.005).

interaction (NCI) analysis (See Figure 3b and 3d). These theoretical findings could explain the experimental observation that **Sc-3** showed higher enantioselectivity than **Sc-2**. These results stand in contrast with the conventional model for enantio-induction in chiral Cp-ligated metal catalysts, in which only steric repulsion was usually taken into account. This work has been published in *Angew. Chem. Int. Ed.* **2025**, *137*, e202419567.

(2) Hydroamination of alkenes with dinitrogen and titanium polyhydrides

Dinitrogen (N_2) is the most abundant constituent in Earth's atmosphere and an easily accessible natural resource, but extremely inert under ordinary conditions. Industrially, N_2 is converted to ammonia (NH_3) through the Haber–Bosch process by hydrogenation with dihydrogen (H_2) on solid catalysts under harsh conditions (350−550 °C, 150−350 atm), which represents the only commercial process using N_2 gas as a feedstock. Currently, NH3 produced by the energy-intensive Haber–Bosch process serves as the sole nitrogen source for industrial preparation of nitrogen-containing organic compounds. The development of methods for direct conversion of N_2 into nitrogen-containing organic compounds under mild conditions is of significant importance and economic and environmental interest to provide simpler and more straightforward processes with a reduced carbon footprint.

Alkyl amines represent an important class of chemicals with various applications. In industry, alkyl amines are mainly produced by dehydrogenative coupling of alcohols with primary or secondary amines, reductive amination of ketones or aldehydes, or nitrilation of carboxylic acids with NH_3, followed by hydrogenation1. All these synthetic routes rely on the use of NH_3 or NH_3-derived nitrogen sources. In addition to the nitrogen source, the carbon sources for the preparation of alkyl amines also require some functional groups, such as hydroxyl or carbonyl groups, to promote carbon–nitrogen (C–N) bond formation with nitrogen sources, and these functional groups are generally prepared from hydrocarbons such as alkenes. The direct use of N_2 and abundant non-activated alkenes as feedstocks for the synthesis of alkyl amines is therefore of great interest but remains unknown.

Extensive studies on transition-metal-mediated direct conversion of N_2 into nitrogen-containing organic compounds have been carried out. Typically, N_2 needs to be initially reduced to activated nitrogen species, which then react with reactive carbon sources. The carbon sources in such reaction processes are largely limited to carbon electrophiles. By contrast, N_2 functionalization with simple hydrocarbons remains a challenge. Recently, we report the direct hydroamination of non-activated alkenes with N_2 mediated by the trititanium polyhydride complex $[\{(C_5Me_4SiMe_3)Ti\}_3(\mu_3\text{-}H)(\mu\text{-}H)_6]$ (**1**), leading to the formation of the corresponding alkyl amines (Figure 4).

To have a better understanding about N_2 activation and N–C bond formation by **4a**, DFT calculations were performed. The most favourable pathways are shown in Figure 5. The coordination of N_2 to the Ti3 atom in **4a** gives **A**, in which the reductive C1–H2 coupling via transition-state **TS1** results in the formation of the $\mu\text{-}\eta^1{:}\eta^2$-side-on–end-on dinitrogen species **B** (Figure 5a). The N=N double bond in **B** could be further reduced to a N–N single bond by the Ti(III) species accompanied by the Ti1–H1 bond cleavage and Ti1–C2 bond formation to yield **C**. The reductive elimination of H1 and H4 via **TS2** would give **D** with release of H2. Subsequently, rearrangement of the dinitrogen unit in **D** takes place to afford a more thermodynamically stable complex **6**, which is in good agreement with experimentally observed complex **6**. The N1–N2 bond cleavage in **6** then occurs via **TS4** to give the dinitride complex **E**. This process is significantly exergonic by 19.5 kcal mol−1. Thereafter, the N1−C2 bond formation readily takes place to give **F**, which is then transformed to **5** through reorientation of the C1=C2 unit, supporting the experimentally

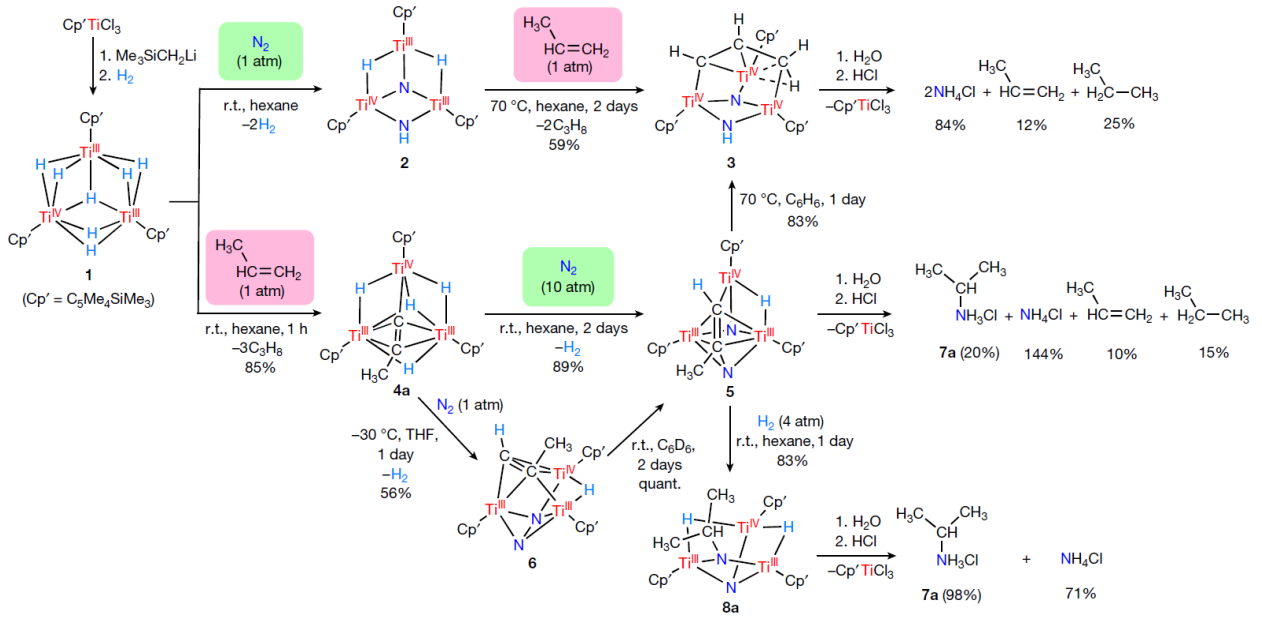


Figure 4. Activation and transformation of propylene and N_2 in a trititanium hydride framework **1**.

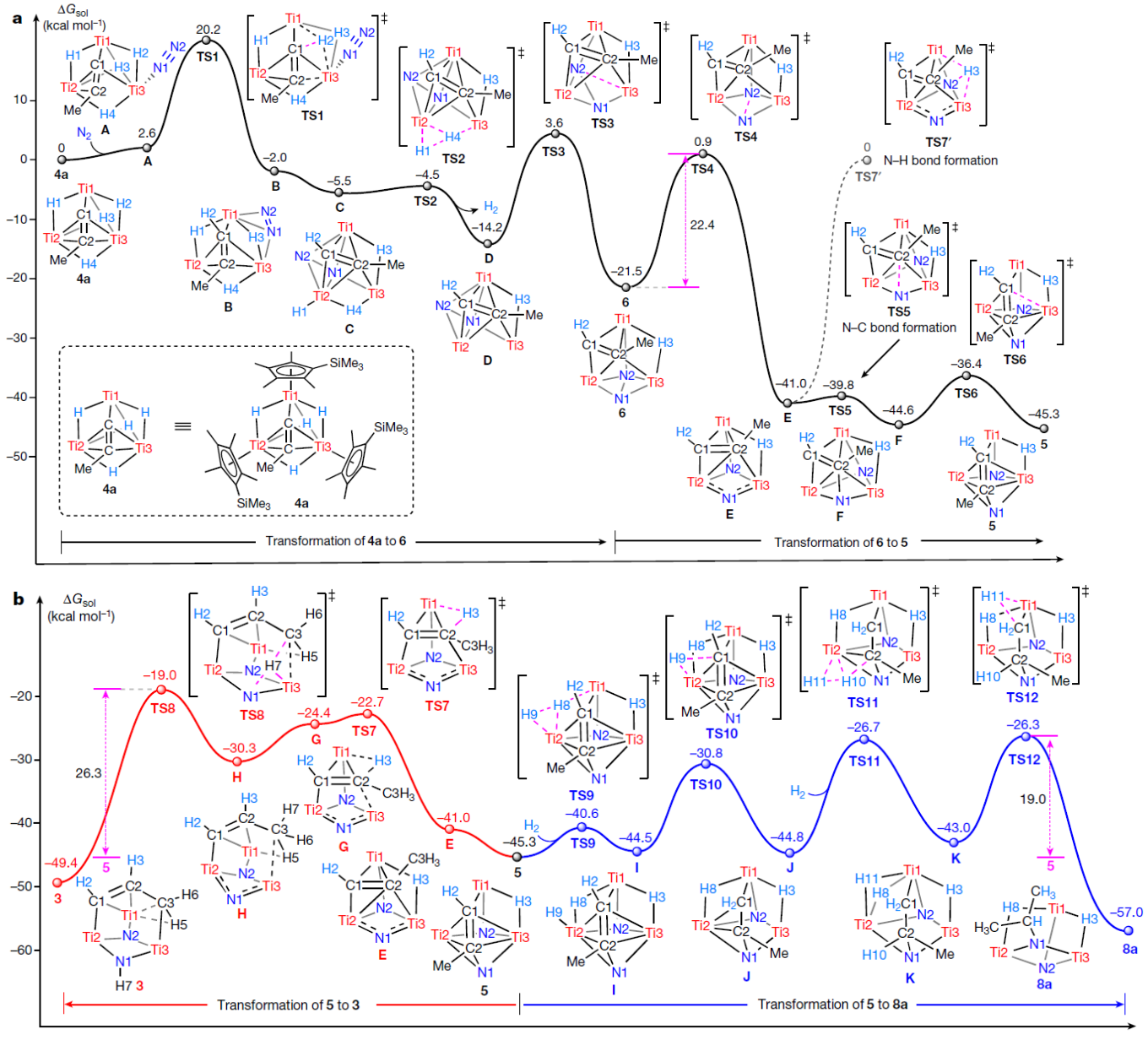


Figure 5. Computational analysis for N_2 activation and N–C bond formation from **4a** to **5** and further reaction of **5**.

observed complex **5**. The rate-determining step is the cleavage of the N1–N2 bond with an energy barrier of 22.4 kcal mol^{-1}, which is in good agreement with the experimental result ($\Delta G(298.15\text{K})^{\ddagger}$ = 23.7 kcal mol^{-1}; ΔG, the relative Gibbs free energy) obtained in the kinetic studies. It is also worth noting that the formation of an N–H bond in **E** requires overcoming a much higher energy barrier (compare **TS7′**, 41.0 kcal mol^{-1}) than that for the N1–C2 bond formation (**TS5**, 1.2 kcal mol^{-1}) in agreement with the experimental observations. The transformation of **5** to **3** has also been investigated by density functional theory calculations (Figure 5b, left). Conversion of **5** to **E** could easily take place (see also Figure 5a). The C2–H3 bond formation in **E** via transition-state **TS7** would give **G**, which could easily isomerize to **H**. The migration of a methyl hydrogen atom (H7) in the propenyl unit to the N1 nitride atom in **H** via transition-state **TS8** would afford the imide–nitride complex **3**. The whole process from **5** to **3** requires overcoming an energy barrier of 26.3 kcal mol^{-1}, which is significantly higher than that of the rate-determining step (22.4 kcal mol^{-1}) in the formation of **5** from **4a** and N_2. These results are in agreement with the experimental observation that the kinetically favourable **5** was exclusively formed in the reaction of **4a** with N_2 at room temperature, whereas **5** was converted to the thermodynamically stable **3** at high temperature. The reaction of **5** with H_2 may proceed through H_2 addition to the Ti2 and Ti1 atoms via **TS9** with an energy barrier of 4.7 kcal mol^{-1}, giving intermediate **I** in which one (H8) of the two newly formed hydride ligands bridges the Ti1 and Ti2 atoms and the other hydride (H9) is terminally bonded to Ti2 (Figure 5b, right). Addition of the Ti2–H9 species to the C1=C2 unit in **I** would give **J**, which upon reaction with another molecule of H_2 could yield **K**. The reductive coupling of H11 and C1 in **K** may yield the more thermodynamically stable isopropylimide complex **8a**, in accord with the formation of the experimentally observed complex **8a**. Overall, the formation of **8a** from **5** and H_2 needs to overcome an energy barrier of 19.0 kcal mol^{-1}, which is much lower than that in the conversion of **5** to **3** ($\Delta G^{\ddagger}$ = 26.3 kcal mol^{-1}). These results well corroborate the selective formation of **8a** in the reaction of **5** with H_2 at room temperature. This work has been published in *Nature* **2024**, *632*, 307-312.

4. Conclusion

(1) By using a chiral half-sandwich scandium catalyst with an appropriately substituted cyclopentadienyl ligand, we have successfully achieved the first enantioselective [3+2] annulation of aromatic aldimines with alkynes *via* C–H activation. This protocol offers a straightforward and atom-efficient route for the selective synthesis of a new family of chiral 1-aminoindene derivatives from readily accessible substrates. Computational analyses reveal that an attractive noncovalent C–H···π interaction between the *tert*-butyl substituent on the Cp ligand of the catalyst and the phenyl ring of an aromatic aldimine substrate plays a crucial role in achieving a high level of enantioselectivity.

(2) By using a trititanium hydride complex **1**, we have achieved direct hydroamination of non-activated alkenes with N2 for the synthesis of alkyl amines. Our results demonstrate that a multinuclear hydride framework such as **1** can serve as an excellent platform for N2 functionalization with simple hydrocarbons such as non-activated alkenes. We hope that this work encourages further efforts in exploring hydroamination of various hydrocarbons with N2 in multinuclear hydride frameworks and developing catalytic processes for the synthesis of amines using N2 and simple hydrocarbons as starting materials.

5. Schedule and prospect for the future

In the following FY2025, 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.

6. If no job was executed, specify the reason.

Usage Report for Fiscal Year 2024

Fiscal Year 2024 List of Publications Resulting from the Use of the supercomputer

1. Aniket Mishra, Jiameng Hu, Xuefeng Cong*, Qingde Zhuo, Masayoshi Nishiura, **Gen Luo***, Zhaomin Hou*. Enantioselective [3+2] Annulation of Aldimines with Alkynes by Scandium-Catalyzed C–H Activation. *Angew. Chem. Int. Ed.* **2025**, *137*, e202419567.

2. Takanori Shima*, Qingde Zhuo, Xiaoxi Zhou, Ping Wu, Ryota Owada, **Gen Luo***, Zhaomin Hou*. Hydroamination of alkenes with dinitrogen and titanium polyhydrides. *Nature* **2024**, *632*, 307-312.