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

The formation of carbon-carbon (C–C) bond is the fundamental reaction for the construction of complex organic molecules. Among possible approaches, the catalytic C–H alkylation through C–H bond addition to alkenes has attracted considerable interest from synthetic organic chemists in past decades because this method is, in principle, one of the most straightforward and atom-economical protocols for construction of C–C bond to achieve the assembly of organic molecules. In this content, a number of studies have been reported with various transition-metal catalysts. It is worth noting that rare-earth (Sc, Y, and lanthanide) alkyl complexes could serve as a unique platform for C–H alkylation of various heteroatom-containing substrates such as sulfides pyridines anisoles, anilines, aldimines, amines, quinolines, imidazoles with alkenes and alkynes, featuring high regio- and stereoselectivity, broad substrate scope, excellent functional group tolerance, which are often superior or complementary to those of transition-metal catalysts due to their unique properties. In such field, Prof. Zhaomin Hou's group (Advanced Catalysis Research Group & Organometallic Chemistry Laboratory, RIKEN) has achieved large amounts of excellent works. Given the high importance of rare-earth catalyzed C–H alkylation, exact mechanistic understandings of those reactions are in great demand, which would be helpful for improving the reactivity, activity, and selectivity of the reactions as well as for designing more efficient catalysts and new reactions. However, it is often difficult to isolate and detect intermediates during many chemical reactions experimentally. Density functional theory (DFT) calculation as a powerful tool play an important role in exploring chemical reaction mechanisms. In the past few years, with the collaboration with Prof. Hou's group, I have made many efforts on mechanism of rare-earth catalyzed C-H functionalization, which effectively promoted the development of the reactions (e.g. *J. Am. Chem. Soc.* **2020**, *140*, 18128; *Organometallics* **2019**, *38*, 1887; *Chem. Sci.* **2016**, *7*, 6429; *Organometallics* **2017**, *36*, 1557). Nowadays, Prof. Hou and co-workers keep making effort to develop new C-H functionalization reactions, and the deep understanding of these new reactions at the molecular level are urgently required. In the last FY2021, with the aid of RIKEN's supercomputer system, some important results have been achieved and published in SCI journals.

2. Specific usage status of the system and calculation method

In the last FY2021, 65% computing resources of BWMPC unit and 100% computing resources of GWACSL unit were used for my Quick Use project. All calculations were performed by Gaussian 16 software together with DFT methods.

3. Result

(a) Sc-Catalyzed Enantioselective C–H Alkenylation of Ferrocenes with Alkynes

Ferrocene and its derivatives have been the subject of extensive studies since the discovery of ferrocene in the early 1950s, because of their fascinating structural features and properties. In particular, ferrocenes possessing planar chirality are of great interest and importance in the fields of asymmetric catalysis and materials science. Therefore, the development of efficient protocols to introduce planar chirality into the ferrocene backbone has attracted intense attention over the past decades. In view of the high potential of chiral hybrid olefin ligands containing both a heteroatom and an olefin unit in asymmetric catalysis, planar-chiral ferrocenes bearing both *N*-heterocycle and alkene functionalities are of great interest. In principle, the asymmetric C–H addition of *N*-heterocycle substituted ferrocenes to alkynes could be a straightforward and 100% atom-efficient route for the synthesis of planar-chiral ferrocenes bearing N/alkene functionalities. However, despite extensive studies and recent advances in C–H activation and transformations, the enantioselective C–H alkenylation of ferrocenes with alkynes has remained a challenge to date because of the lack of suitable chiral catalysts.

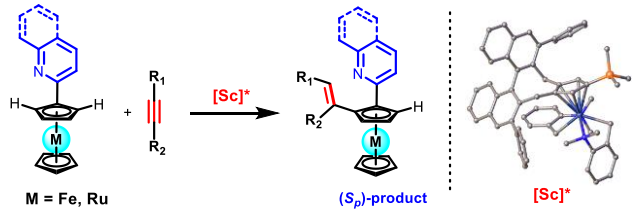

Fig. 1. Asymmetric C–H Addition of Ferrocenes to Alkynes.

It has been previously reported that the reaction of amine-substituted ferrocenes with diphenylacetylene in the presence of a chiral palladium catalyst gave the corresponding alkyne-annulated ferrocene products, while a straightforward C–H alkenylation product was not obtained. The reaction of an isoquinoline-substituted ferrocene with diphenylacetylene by a chiral iridium catalyst afforded the C–H alkenylation product, but no significant enantioselectivity was observed although the analogous asymmetric C–H alkylation with alkenes worked well. Search for new catalysts for the asymmetric C–H alkenylation of ferrocenes with alkynes is therefore of much interest and importance. Here we report for the first time the highly enantioselective C–H alkenylation of quinoline- and pyridine-substituted ferrocenes with alkynes by a chiral scandium catalyst (Fig. 1).

To gain more information on the reaction mechanism, we performed DFT calculations (Fig. 2). Some representative energy data together with a possible reaction mechanism for the reaction of **1a** with **2a** by **Ph-TMS-Sc** are shown in Figure 2. The deprotonative C–H activation at the C8 position of the quinoline unit in **1a** by the Sc–R species in **cat-Sc** followed by coordination of another molecule of **1a** to the metal center would give intermediate **A** by overcoming an energy barrier of $\Delta G^{\ddagger}$ = 25.4 kcal/mol. The intramolecular C – H activation of the quinoline-substituted Cp unit of the coordinated **1a** in **A** then gives (R_p)-**B** ($\Delta G^{\ddagger}$ = 20.1 kcal/mol). This process is much favored over the alkyne insertion into the Sc–quinolyl bond in **A** to give **D** ($\Delta G^{\ddagger}$ = 25.8 kcal/mol). The direct C(Cp)–H activation of **1a** by **cat-Sc** to afford (R_p)-**B** is also possible by overcoming a comparable energy barrier (via **TS1**, $\Delta G^{\ddagger}$ = 25.2 kcal/mol). The replacement of **1a** with **2a** followed by C≡C insertion into the Sc–Cp σ-bond in (R_p)-**B** could give (S_p)-**C** (via **TS2**, $\Delta G^{\ddagger}$ = 21.1 kcal/mol). Subsequently, the hydrogen abstraction of **1a** by the Sc – vinyl bond in (S_p)-**C** would release the final product (S_p)-**3a** ($\Delta G^{\ddagger}$ = 25.0 kcal/mol) and regenerate (R_p)-**B** after coordination of another molecule of **1a**. The direct formation of enantiomeric isomer (S_p)-**B** by the reaction of **cat-Sc** with **1a** requires a much higher energy barrier (via **TS1"**, $\Delta G^{\ddagger}$ = 29.7 kcal/mol). Although (S_p)-**B** could be alternatively generated from (R_p)-**B** ($\Delta G^{\ddagger}$ = 19.6 kcal/mol), the alkyne insertion into (S_p)-**B** to give (R_p)-**C** (via **TS2"**, $\Delta G^{\ddagger}$ = 27.4 kcal/mol) is less favored compared to the conversion of (S_p)-**B** to (R_p)-**B** ($\Delta G^{\ddagger}$ = 19.7 kcal/mol).

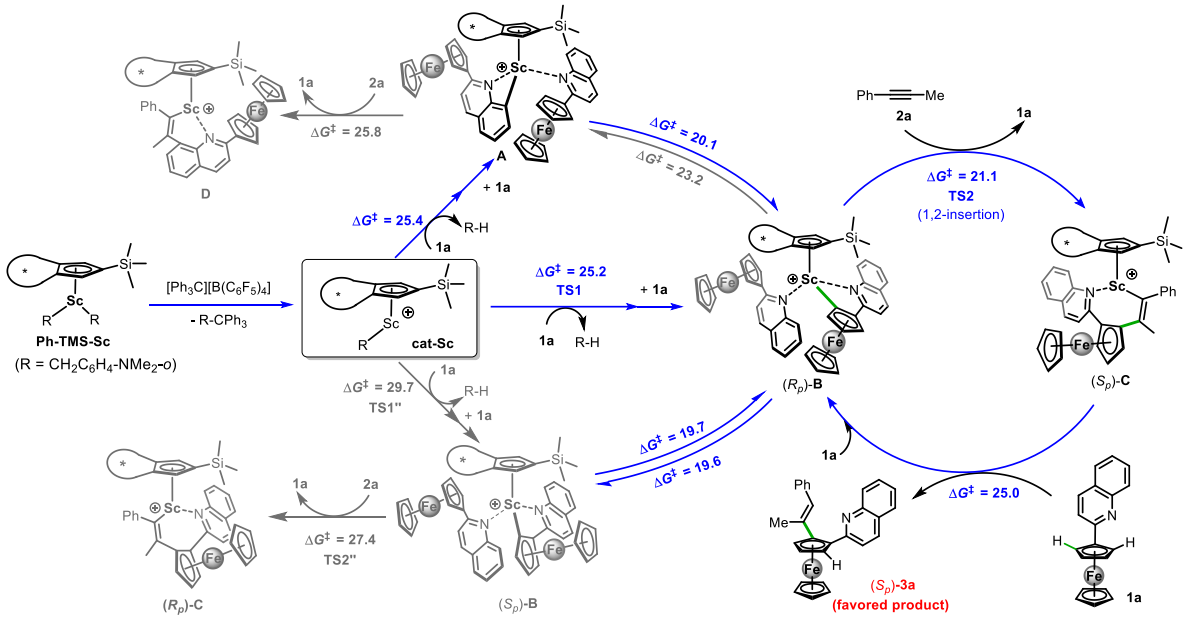

Fig. 2. Possible mechanism of enantioselective C–H alkenylation of **1a** with **2a** by **Ph-TMS-Sc**.

This protocol features broad substrate scope, high enantioselectivity, and 100% atom efficiency, affording a new family of planar-chiral ferrocenes bearing N/alkene functionalities. This work has been published as *J. Am. Chem. Soc.* **2021**, *143*, 2470–2476.

(b) Theoretical Studies of Rare-Earth Catalyzed [3 + 2] Annulation of Aromatic Aldimine with Styrene

Aminoindane moieties play an important role in organic chemistry and pharmaceutical chemistry research, especially for multi-substituted chiral 1-aminoindane frameworks. Among the possible approaches to the synthesis of 1-aminoindane,2 catalytic C(sp^2)–H activation triggered tandem [3 + 2] annulation of aromatic aldimines with olefins has been studied extensively due to its 100% atomic economy. In most previous reports, transition metal complexes, such as rhodium, rhenium, iridium, cobalt, manganese and so forth, were used as catalysts for the [3 + 2] annulation of aromatic aldimines with olefins induced by C(sp^2)–H activation to synthesize 1-aminoindanes. In those contents, the stereoselectivity of the reactions is usually controlled by changing additives, temperature, solvents or the substrates. Very recently, Hou and coworkers reported that the diastereodivergent [3 + 2] annulation of aromatic aldimines with alkenes catalyzed by half-sandwich rare-earth complexes and the diastereodivergence is achieved by fine-tuning ligand/metal combination of the catalysts (Fig. 3). As shown in Fig. 3, in the reaction of tert-butyl benzaldimine (**1a**) with styrene (**2a**), cis-diastereoisomer product could be exclusively obtained when C_5Me_4H ligand was used for yttrium catalyst (**Y-1**, *trans*-**3a**/*cis*-**3a** < 1:19). Intriguingly, the $C_5Me_4SiMe_3$-ligated scandium catalyst **Sc-2** could completely reverse the diastereoselectivity compared to analogous yttrium catalyst **Y-1**, giving trans-diastereoisomer product exclusively (*trans*-**3a**/**cis**-*3a* > 19:1).

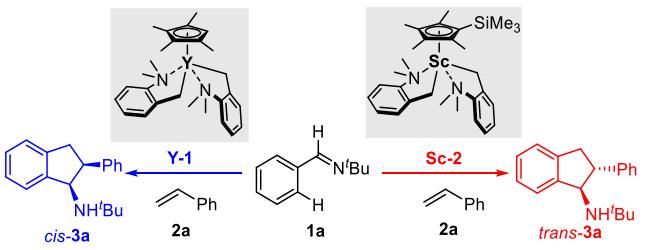

Fig. 3. Rare-earth catalyzed [3 + 2] annulation of benzaldimine with styrene.

Considering the importance of 1-aminoindane synthesis and the fascinating diastereoselectivity,

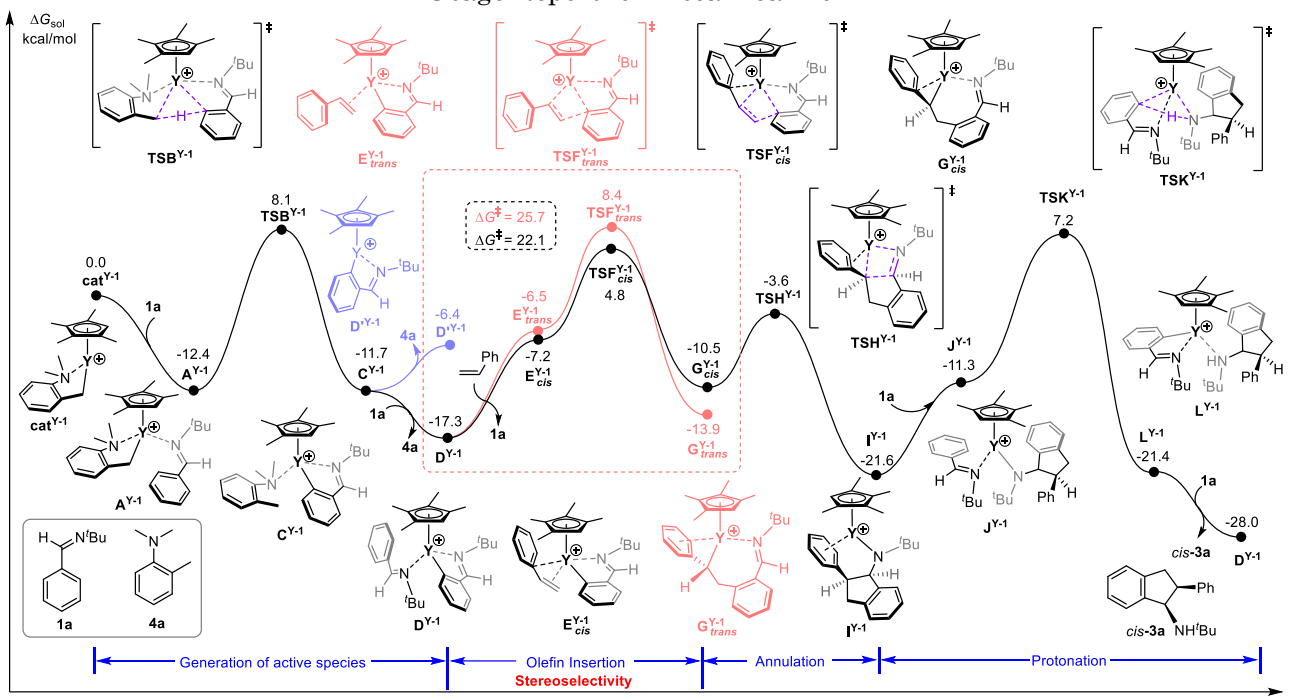

Fig. 4. Energy profiles of **Y-1**-catalyzed [3 + 2] annulation of *N*-tert-butyl benzaldimine (**1a**) with styrene.

we have performed DFT calculations to reveal the mechanism and the origin of diastereoselectivity in rare-earth catalyzed [3 + 2] annulation of aromatic aldimines with olefins. The in-depth mechanistic understanding of such catalyst-controlled reversal of stereoselectivity is in great demand and the related results could obviously facilitate the development of new stereospecific and stereoconvergent annulation reactions based on the rare-earth-mediated C–H activation.

As shown in Fig. 4, the mechanism of [3 + 2] annulation of *N*-tert-butyl benzaldimine (**1a**) with styrene catalyzed by **Y-1** were calculated. Computational results show that the reaction generally involves four steps, *viz.*, generation of benzaldimine-coordinated species as the catalytically active species, olefin insertion through a potential diastereoselective manner, the intramolecular nucleophilic addition of the M–C bond to the C=N (cyclization), and finally, the protonation via the C(sp^2)–H activation of another molecule of aromatic aldimine giving the product 1-aminoindane and regenerating the catalytically active species. It's worth noting that the noncovalent interactions, such as C–H···π and metal···π interactions, play an important role in stabilizing the key transition state or intermediate. As for the origin of diastereoselectivity, it is found that the *cis*-diastereoselectivity in **Y-1** case could be ascribed to the smaller orbital energy gap, resulting in stronger interaction between the catalyst and styrene moieties during the styrene insertion. In the case of **Sc-2** catalyst, the repulsion between the bulky $C_5Me_4SiMe_3$ ligand and aldimine group induces the formation of a C–H···π interaction between the N^{t}Bu group and benzene ring in *trans*-diastereoselectivity manner, and thus stabilizes the *trans*-selective transition state.

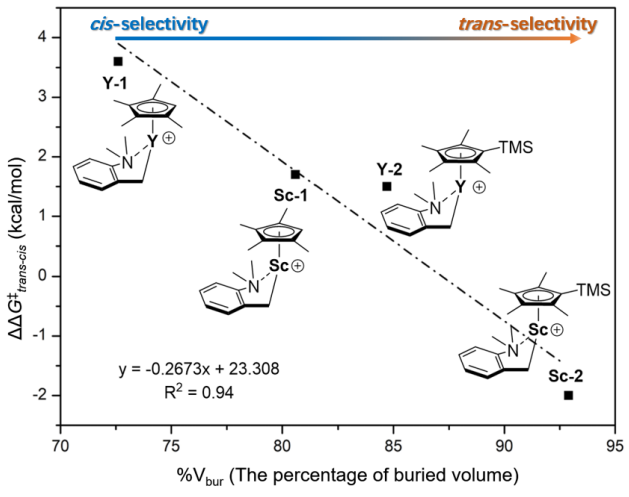

Fig. 5. The linear relationship between the value of $\Delta\Delta G^{\ddagger}_{trans\text{-}cis}$ and the percentage of buried volume of metal center ($\%V_{Bur}$) in cationic species of catalysts.

It is interesting to note that a good linear relationship was found between the energy barrier difference between the *trans*- and *cis*-insertion manners and the percentage of buried volume of metal center in the cationic species of catalysts (Fig. 5). Such a correlation indicates that the *cis*-selectivity is preferred when using the catalyst with less steric hindrance, and the contrary is also vice versa. This is mainly due to that the steric hindrance in catalyst would change the interaction strength between the catalyst and styrene moieties via C–H···π interaction. The diastereoselectivity is controlled by both the steric and electronic factors and the stereospecific product could therefore be obtained by fine-tuning the ligand/metal combination of the catalysts. The results presented here could add better understanding to the mechanism and the origin of diastereoselectivity of rare-earth catalyzed [3 + 2] annulation of aromatic aldimines with alkenes and would be helpful for further development of rare-earth catalyzed diastereoselective reactions. This work has been published as *J. Org. Chem.* **2021**, *86*, 4236–4244.

(c) Sc-Catalyzed Dearomative Annulation of Quinolines with Alkynes

Developing protocols that enable the construction of molecular complexity from simple starting materials in an atom-efficient and enantioselective manner is a long-standing goal and key challenge in organic synthesis. Organic molecules containing three-dimensional architectures such as spiro compounds have received much attention, as the spiro-conformational rigidity can provide unique opportunities for tapping into a three-dimensional chemical space and may play an important role in medicinal chemistry and drug discovery. In particular, spiro-hydroquinolines containing a quaternary carbon stereocenter with an unprotected N–H group are of much interest, as hydroquinolines are important structural motifs in many natural products, pharmaceuticals and biologically active molecules. In principle, the catalytic asymmetric dearomative annulation of substituted quinolines is the most efficient and straightforward route for the synthesis of chiral spiro-hydroquinolines. However, despite extensive studies and recent advances in the dearomatization of quinolines and related *N*-heteroaromatics, the asymmetric construction of an N–H free spiro-hydroquinoline architecture by the dearomatization of a quinoline skeleton has remained a challenge to date because of difficulty in asymmetric addition to the *ipso*-carbon of a substituted quinoline moiety. Recently, we report our discovery of an unprecedented dearomative [3+2] annulation of 2-arylquinolines with alkynes by half-sandwich scandium catalysts (Fig. 6).

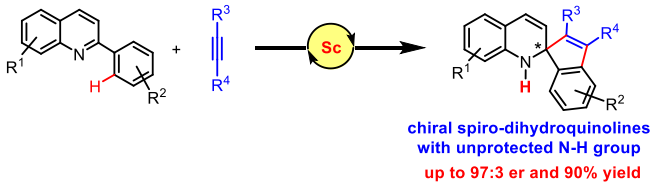

Fig. 6. Sc-catalyzed asymmetric [3 + 2] spiro-annulation of 2-arylquinolines with alkynes.

This transformation offers an efficient and selective route for the synthesis of a new family of spiro-dihydroquinoline derivatives containing a quaternary carbon stereocenter with an unprotected N–H group. DFT calculations revealed that the reaction proceeded formally through the C–H activation of the 2-aryl substituent in the quinoline substrate by a scandium alkyl species followed by alkyne insertion into the Sc–aryl bond and the subsequent 1,2-addition of the resulting scandium alkenyl species to the C=N group (Fig. 7). Remarkably, this transformation can be achieved in an asymmetric fashion by using a chiral half-sandwich scandium catalyst, affording a series of chiral spiro- hydroquinoline derivatives in high yields and high enantioselectivity. The mechanistic details of this transformation have also been clarified by DFT studies (Fig. 8).

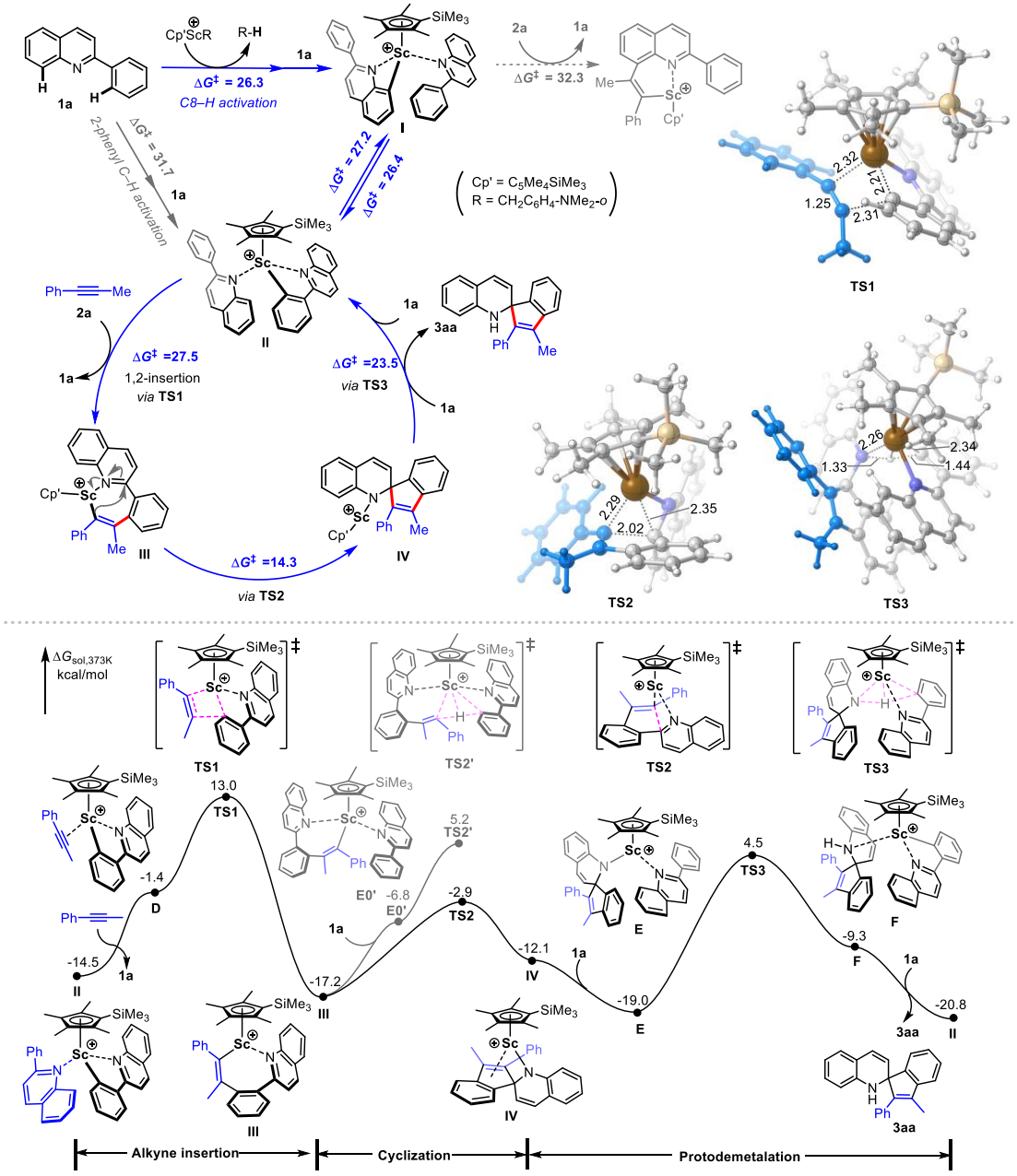

Fig. 7. Calculated mechanism of the spiro-annulation of **1a** with **2a** by **Sc-1**.

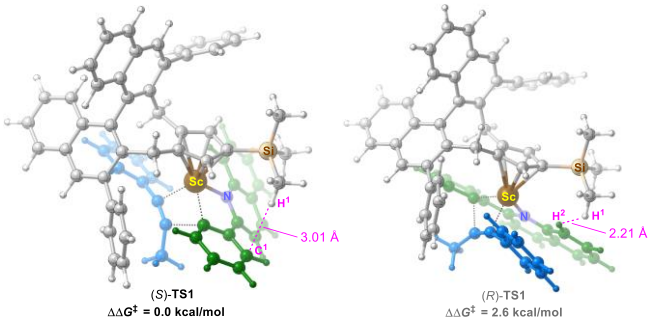

Fig. 8. Computed enantioselectivity-controlling transition states (*S*)-**TS1** and (*R*)-**TS1** for the asymmetric dearomative annulation of **1a** with **2a** by **Ph-TMS-Sc**.

In summary, by using half-sandwich scandium catalysts we have succeeded in developing the dearomative spiro-annulation of a wide range of 2-arylquinolines with diverse alkynes. The reaction is based on a unique combination of the scandium-catalyzed C–H activation, alkyne insertion, and dearomative nucleophilic 1,2-addition of alkenyl species to the C=N unit of a quinoline moiety, standing in sharp contrast with the previously reported late-transition-metal-catalyzed transformation of the similar substrates. This protocol features atom-efficiency, broad substrate scope, high yield, high enantioselectivity, and well-defined reaction mechanism, offering an efficient and selective route for the synthesis of a new family of N–H free spiro-dihydroquinoline derivatives which are of great interest and

importance in medicinal chemistry and drug discovery but were previously difficult to access by other means. Moreover, this work may also help guide further development of new catalytic systems for the construction of three-dimensional molecular architectures or other molecular complexities from simple planar starting materials. This work has been published as *J. Am. Chem. Soc.* **2021**, *143*, 20462−20471.

4. Conclusion

(a) With the aid of DFT calculations, we developed a method for the highly enantioselective C−H alkenylation of quinoline-substituted ferrocenes with alkynes by a half-sandwich scandium catalyst. This protocol features broad substrate scope, high enantioselectivity, and 100% atom efficiency, selectively affording a new family of planar-chiral ferrocenes bearing *N*alkene functionalities.

(b) DFT calculations revealed the mechanism of rare-earth catalyzed diastereodivergent [3 + 2] annulation of benzaldimine with styrene. The reaction mainly involves generation of active species, olefin insertion, cyclization, and protonation steps. The preferred *cis*-diastereo selectivity could be ascribed to more efficient orbital interaction, while the crowded space will induce the formation of a C−H···π interaction between the N^{t}Bu group and benzene ring in *trans*-diastereoselectivity manner, and thus stabilizes the *trans*-selective transition state.

(c) A synthetic method of Sc-catalyzed asymmetric dearomative spiro-annulation of quinolines with alkynes has been developed. DFT calculations revealed that the reaction proceeded through the C–H activation of the 2-aryl substituent in a quinoline substrate by a scandium alkyl (or amido) species followed by alkyne insertion into the Sc–aryl bond and the subsequent dearomative 1,2-addition of the resulting scandium alkenyl species to the C=N unit in the quinoline moiety. This work opens a new avenue for the dearomatization of quinolines, leading to efficient and selective construction of spiro molecular architectures that were previously difficult to access by other means.

5. Schedule and prospect for the future

In the following FY2022, 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.

Fiscal Year 2021 List of Publications Resulting from the Use of the supercomputer

(1) Shao-Jie Lou, Qingde Zhuo, Masayoshi Nishiura, **Gen Luo***, and **Zhaomin Hou***. Enantioselective C−H alkenylation of ferrocenes with alkynes by half-sandwich scandium catalyst. *J. Am. Chem. Soc.* **2021**, *143*, 2470–2476. (Publication date: Feb. 2021; Impact Factor: 15.419)

(2) Pan Wang, **Gen Luo***, Jimin Yang, Xuefeng Cong, **Zhaomin Hou**, and Yi Luo*. Theoretical Studies of Rare-Earth-Catalyzed [3 + 2] Annulation of Aromatic Aldimine with Styrene: Mechanism and Origin of Diastereoselectivity. *J. Org. Chem.* **2021**, *86*, 4236–4244. (Publication date: Feb. 2021; Impact Factor: 4.354)

(3) Shao-Jie Lou, **Gen Luo***, Shigeru Yamaguchi, Kun An, Masayoshi Nishiura, **Zhaomin Hou***. Modular Access to Spiro-dihydroquinolines via Scandium-Catalyzed Dearomative Annulation of Quinolines with Alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 20462−20471. (Publication date: Nov. 2021; Impact Factor: 15.419)