

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

Transition and rare-earth metal complexes mediated chemical transformations have been received considerable attention in the field of organic synthesis and organometallic chemistry in the last decades. In such field, Prof. Zhaomin Hou's group (Advanced Catalysis Research Group & Organometallic Chemistry Laboratory, RIKEN) has achieved large amounts of excellent works. As we know, an understanding of the exact reaction mechanism is an essential aspect of chemistry in general, 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 investigation of homogeneous chemical reactions, which effectively promoted the development of catalytic/activation reactions (e.g. *Sci. Adv.*, **2017**, *3*, e1701011; *Nat. Commun.*, **2017**, *8*, 1866; *J. Am. Chem. Soc.*, **2019**, *141*, 2713). Nowadays, Prof. Hou and co-workers continue to develop new reactions experimentally, and the good understanding of such new reactions at the molecular level are urgently required. Obviously, DFT calculation is an effective approach to reveal the detailed mechanism and the origins of activity

and selectivity, which could be effective to develop new catalysts and new reactions. In the last FY2020, 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 FY2020, about 753 kilo core*hours were used for my Quick Use project. All calculations were performed by Gaussian 16 software together with DFT methods.

3. Result

(a) Enantioselective Cyanoborylation of Allenes by N-Heterocyclic Carbene-Copper Catalysts

The catalytic multifunctionalization of unsaturated C=C bonds is a straightforward and efficient strategy for the assembly of densely functionalized chemicals from simple starting materials. In view of the tremendous applications of organoboron compounds in various chemical transformations and nitriles as versatile intermediates for the synthesis of many biologically active molecules, fine chemicals, dyes, pigments, and polyamides, the direct cyanoborylation of allenes in an enantioselective fashion, which would lead to the simultaneous installation of both a cyano group and a boryl group into a C=C double bond of the allene substrate, is of particular interest and importance. However, the difunctionalization of the 1,2-orthogonal C=C double bonds in allenes

often suffers from regioselectivity problems. Besides, chemoselectivity issues can also arise due to the simultaneous existence of a number of reactive species. Although several copper-catalyzed enantioselective borylative functionalization reactions of allenes were reported recently, the enantioselective cyanoborylation of allenes has not been achieved yet.

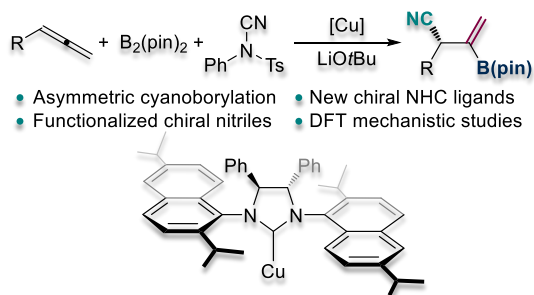


Fig. 1. Catalytic cyanoborylation of allenes.

Herein, we report a copper-catalyzed chemo-, regio-, and enantioselective cyanoborylation of allenes, which afforded β -boryl allyl nitriles efficiently (Fig. 1). The competing hydroboration of the remaining C=C double bonds after cyanoborylation was successfully suppressed. The systematic adjustment of the substituents on the C2 and C6 positions of the naphthalene moieties in our newly prepared chiral N-heterocyclic carbene (NHC) ligands enabled the direct synthesis of valuable enantiopure β -boryl allyl nitriles, which could be readily elaborated into useful organic molecules. This method shows excellent functional group tolerability and is easy to scale up. Computational studies revealed that the regioselectivity of borocupration is governed by both the steric hindrance and electronic effects (Fig. 2). The enantioselectivity of cyanation is attributed to the steric effects of the substituted naphthyl wingtips of the NHC ligand. The current reaction represents an inspiring example of fine-tuning of a ligand enabling selective catalysis for the efficient synthesis of complex

molecules from simple feedstocks. This work has been published in *ACS Catal* (2020, 10, 11685-11692) and was selected as ACS Editors' Choice.

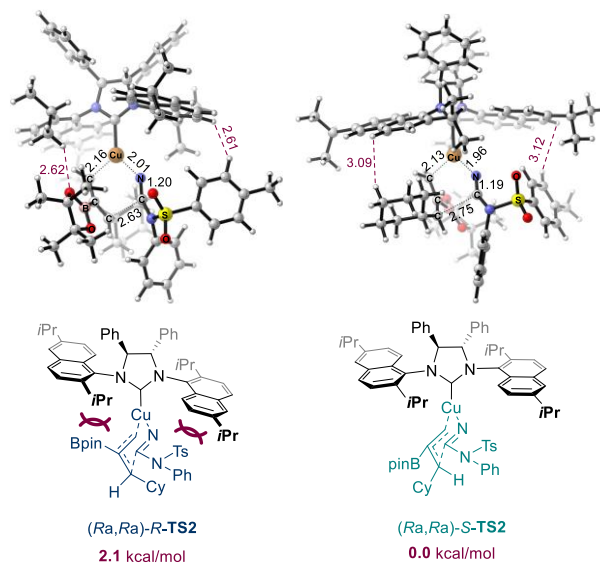


Fig. 2. Calculated the transition states of (R_a,R_a) -*R*-TS2 and (R_a,R_a) -*S*-TS2.

(b) Regiodivergent C–H Alkylation of Quinolines with Alkenes by Rare-Earth Catalysts

Quinoline is an important structural motif in a large number of pharmaceuticals, agrochemicals, and natural products. Therefore, the development of efficient protocols for the selective synthesis of diversified quinoline derivatives is of much interest and importance. In principle, the regiodivergent C–H alkylation of quinolines with alkenes is an ideal 100% atom-efficient route for the preparation of diverse alkylated quinoline derivatives from the same set of starting materials. However, despite great interest and extensive studies in this area, the regiodivergent C–H alkylation of quinolines with alkenes has not been reported previously. A number of transition metal catalysts have been reported for the C–H alkylation of the pyridine moiety of a quinoline skeleton with alkenes. In contrast, the selective C–H alkylation at the benzene ring (such as the C8 position) of a neutral quinoline molecule has remained unknown to date. A rhodium catalyst was previously reported to enable the C8–H

alkylation of quinoline N-oxides with alkenes, in which the N-oxide unit served as a directing group. This approach required the pre-oxidation of a quinoline precursor, and was limited only to C2-substituent-free quinolines, while C2-substituted quinoline substrates were not applicable probably due to steric hindrance. The direct C8-H alkylation of neutral, N-oxide-free quinolines, especially C2-substituted quinolines has remained a challenge to date.

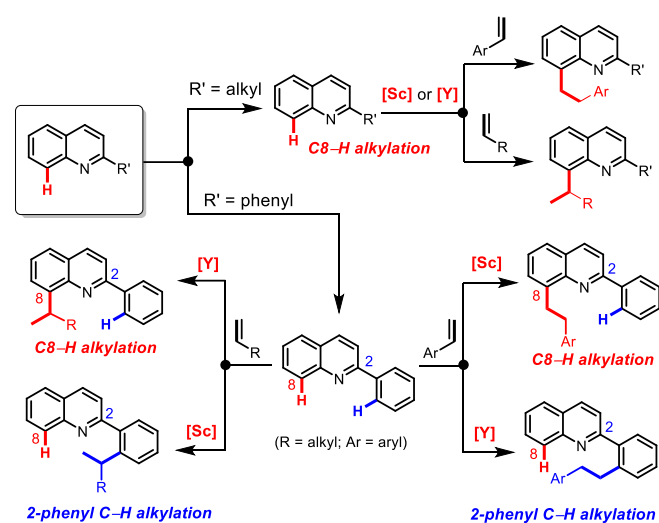


Fig. 3. Regiodivergent C–H alkylation of quinolines with alkenes.

Herein, we report the first regiodivergent C–H alkylation of quinolines with alkenes by half-sandwich rare-earth catalysts (Fig. 3). The regiodivergence was achieved by fine-tuning the metal/ligand combination or steric and electronic properties of the catalysts. The use of a C_5Me_5 -ligated scandium catalyst **Sc-3** for the reaction of quinolines with styrenes and that of a C_5Me_4H -ligated yttrium catalyst **Y-2** for the reaction with aliphatic olefins exclusively afforded the corresponding C8–H alkylation products, thus constituting the first example of direct C8–H alkylation of neutral quinolines. In contrast, the **Sc-3**-catalyzed reaction of 2-aryl quinolines with aliphatic olefins and the **Y-2**-catalyzed reaction with styrenes selectively gave the 2-aryl *ortho*-C–H alkylation products. Based on the catalyst/substrate-controlled regiodivergence, the sequential regiospecific dialkylation of quinolines

with two different alkenes has also been achieved.

Computational studies have well supported the experimental results. The bond dissociation energy (BDE) analysis by DFT suggests that the *ortho*-C–H bond of the phenyl group in 2-phenylquinoline is easier to break than the C8–H bond. In agreement with the BDE analysis, the formation of a phenyl C–H activation species like **I_{Y-2}** is favored in the case of **Y-2**. In contrast, a C8–H activation product like **II_{Sc-3}** is preferred in the case of **Sc-3** because of steric influence. The coordination of one molecule of 2-phenylquinoline to the metal center of the initially formed phenyl C–H activation species **I_{Ln}** and C8–H activation species **II_{Ln}** could easily take place to give the corresponding more stable adduct complexes **I'_{Ln}** and **II'_{Ln}**, respectively. The interconversion of **I'_{Ln}** and **II'_{Ln}** through C–H activation of the quinoline ligand is possible in the case of either **Y-2** or **Sc-3**.

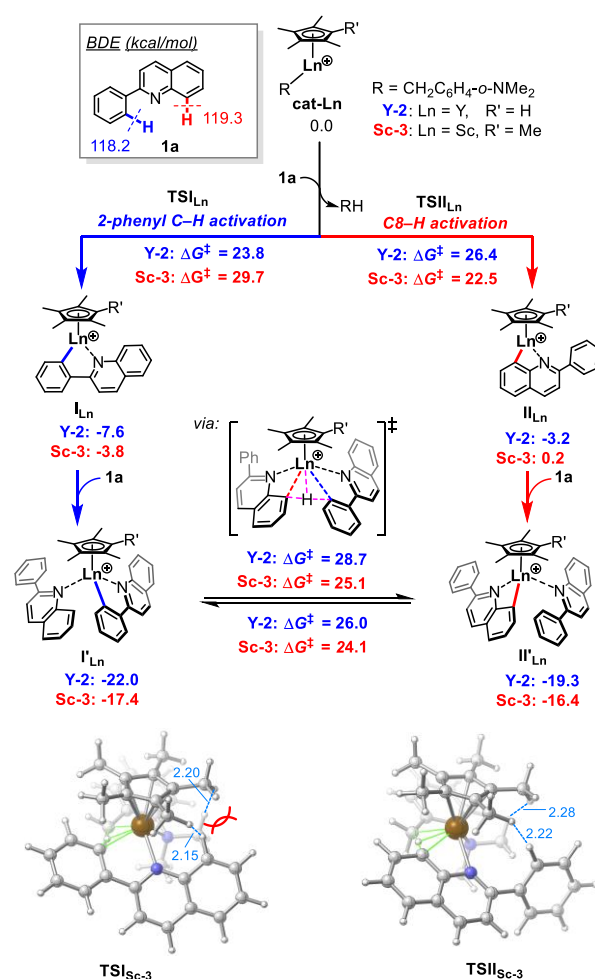


Fig. 4. BDE of C–H bonds in **1a** and calculated scenarios of C–H activation of **1a** by **Y-2** and **Sc-3**.

Usage Report for Fiscal Year 2020

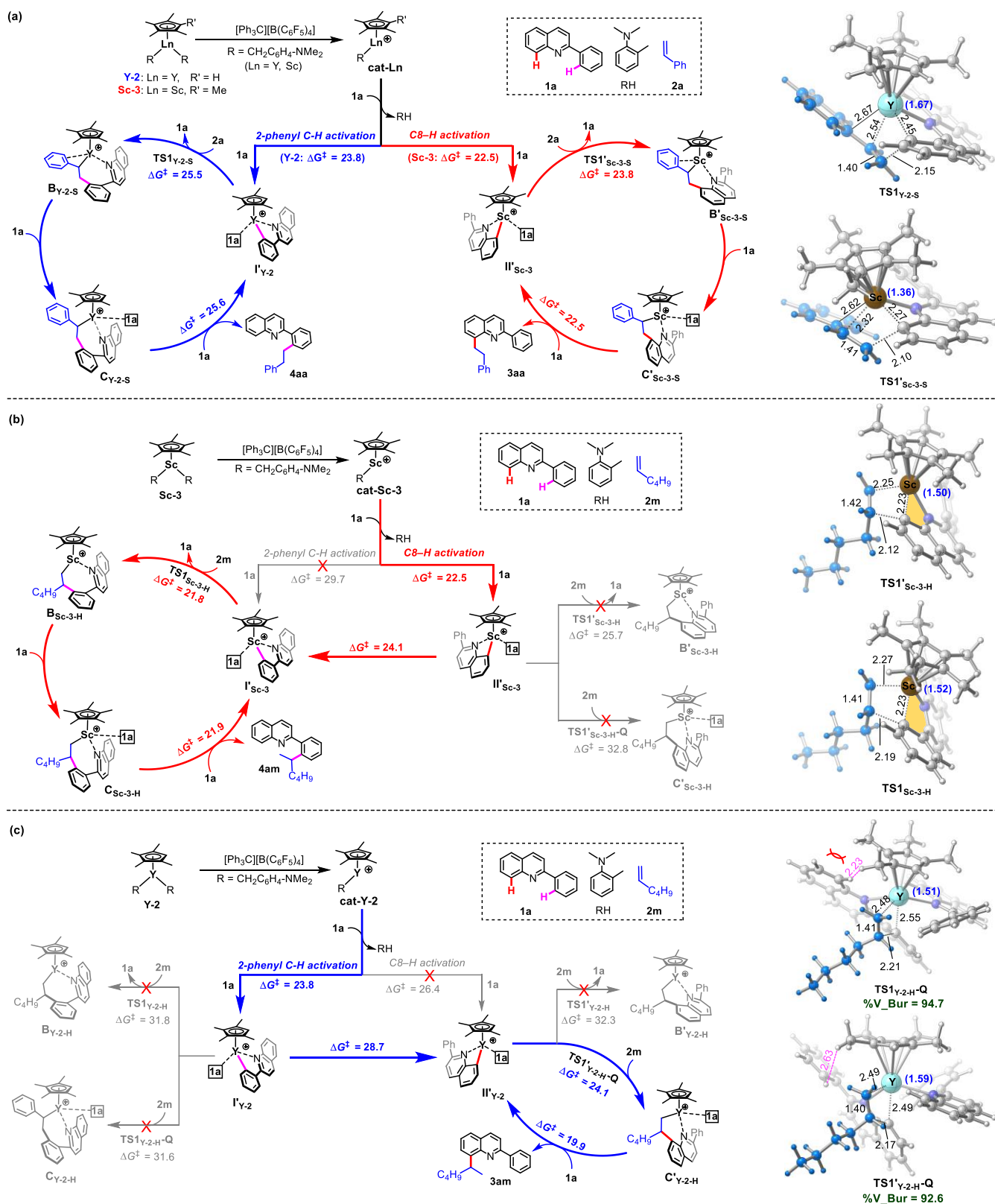


Fig. 5. Computational analyses and possible scenarios of the regiodivergent C–H alkylation of 2-phenylquinoline (**1a**) with styrene (**2a**) and 1-hexene (**2m**) catalyzed by **Y-2** and **Sc-3**. (a) Reaction of **1a** with styrene (**2a**) catalyzed by **Y-2** and **Sc-3**. (b) Reaction of **1a** with 1-hexene (**2m**) catalyzed by **Sc-3**. (c) Reaction of **1a** with 1-hexene (**2m**) catalyzed by **Y-2**.

The regioselectivity for the C–H alkylation reactions is governed not only by the initially generated C–H activation products but also by the

energy barriers for their interconversions as well as by the energy barriers or steric and electronic influences in the subsequent alkene insertion

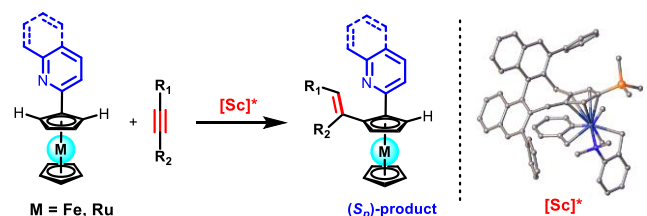
processes (Fig. 5). In the **Y-2**-catalyzed reaction of 2-phenylquinoline with styrene, the insertion of styrene into the phenyl C–H activation species **I'Y-2** easily leads to the formation of the corresponding phenyl C–H alkylation product **4aa**. Analogously, the insertion of styrene into the C8–H activation species **II'Sc-3** smoothly affords the corresponding C8–H alkylation product **3aa** in the case of **Sc-3**. However, in the **Sc-3**-catalyzed reaction of 2-phenylquinoline with 1-hexene, the insertion of 1-hexene into the C8–H activation species **II'Sc-3** is more difficult than the conversion of **II'Sc-3** into the phenyl C–H activation species **I'Sc-3** because 1-hexene is less reactive, and therefore, the insertion of 1-hexene into **I'Sc-3** preferably takes place, leading to the selective formation of the phenyl C–H alkylation product **4am**. In the **Y-2**-catalyzed reaction of 2-phenylquinoline with 1-hexene, the insertion of 1-hexene into the phenyl C–H activation species **I'Y-2** requires overcoming energy barriers higher than that of the conversion of **I'Y-2** into the C8–H activation species **II'Y-2** because of steric and electronic influences. The insertion of 1-hexene into **II'Y-2** may take place without dissociation of the quinoline ligand, thus selectively yielding the C8–H alkylation product **3am**.

This work has not only constituted an efficient protocol for the selective synthesis of diversified quinoline derivatives, but also offered unprecedented insights into the C–H activation and transformation of quinolines, and may help design more efficient, selective or complementary catalysts. This work has been published in *J. Am. Chem. Soc.* (2020, 142, 18128-18137).

(c) Enantioselective C–H Alkenylation of Ferrocenes with Alkynes by Half-Sandwich Scandium Catalyst

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.

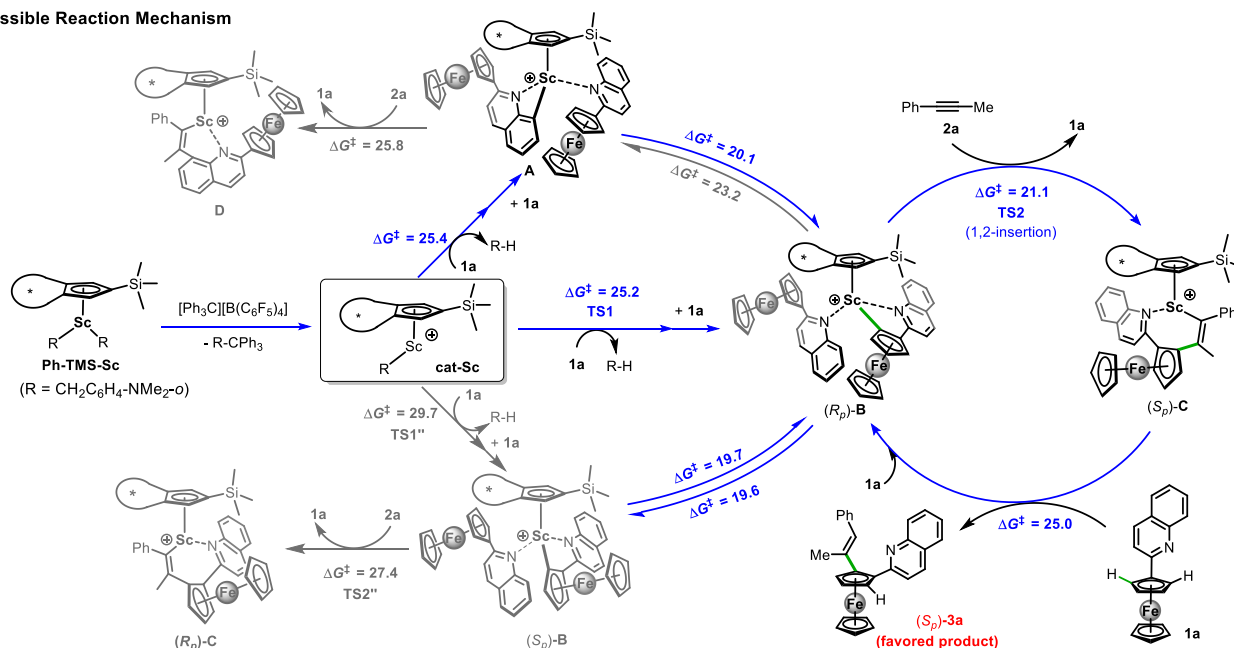


Efficient construction of planar-chiral ferrocenes with N/olefin-functionality
 •High enantioselectivity •High regioselectivity •DFT Mechanistic insight

Fig. 6. 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

a. Possible Reaction Mechanism



b. Transition states

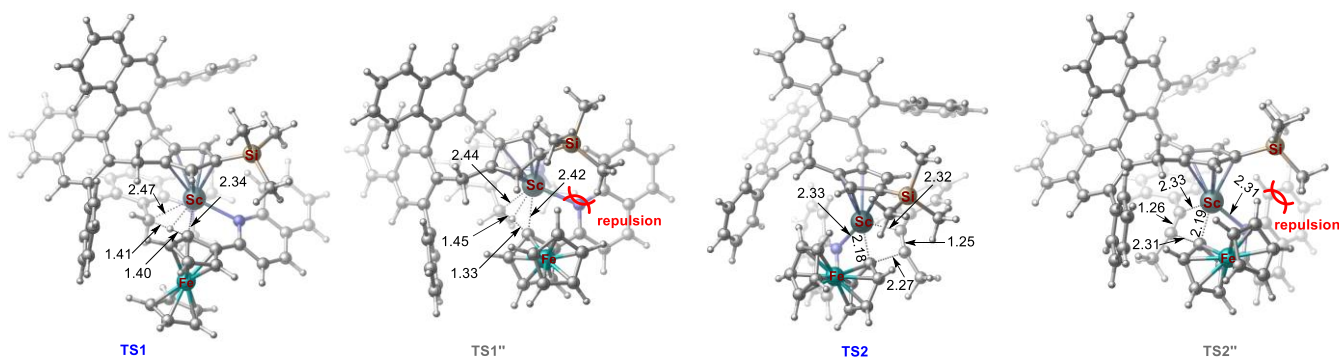


Fig. 7. Possible mechanism of enantioselective C–H alkenylation of **1a** with **2a** by **Ph-TMS-Sc**.

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. 6).

To gain more information on the reaction mechanism, we performed DFT calculations (Fig. 7). 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).

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 in *J. Am. Chem. Soc.* (**2021**, *143*, 2470–2476).

(d) Other works

In addition to the copper-catalyzed cyanoborylation and rare-earth catalyzed C-H alkylation, we have also revealed the theoretical insights into the reactivity of rare-earth/phosphorus Lewis pairs toward polymerization of conjugated polar alkenes (*Inorg. Chem. Front.*, **2020**, *7*, 4600-4610). In addition, the mechanisms of dinitrogen activation by a diniobium tetrahydride (*Inorg. Chem.*, **2020**, *59*, 4626–4633) and a trinuclear chromium hydride complexes (*J. Am. Chem. Soc.*, **2020**, *142*, 9007–9016) were computationally investigated.

4. Conclusion

(a) We reported a copper-catalyzed chemo-, regio-, and enantioselective cyanoborylation of allenes, which afforded a family of valuable enantiopure β -boryl allyl nitriles. The high enantioselectivity was achieved by installing of appropriate substituents at the C2 and C6 positions of the naphthyl groups in our newly synthesized *N*-heterocyclic carbene (NHC) ligands. The reaction mechanism has been clarified by some stoichiometric reactions and computational studies.

(b) We reported the first regiodivergent C-H alkylation of quinolines with alkenes by half-sandwich rare-earth catalysts. The regiodivergence was achieved by fine-tuning the metal/ligand combination or steric and electronic properties of the catalysts. The use of the C₅Me₅-ligated scandium catalyst **Sc-3** for the reaction of quinolines with styrenes and that of the C₅Me₄H-ligated yttrium catalyst **Y-2** for the reaction with aliphatic olefins exclusively afforded the corresponding C8-H alkylation products, thus constituting the first example of direct C8-H alkylation of neutral quinolines.

(c) We reported for the first time the highly enantioselective C-H alkenylation of quinoline- and pyridine-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. The mechanistic details have been clarified by DFT analyses. The use of a quinoline/alkene-functionalized ferrocene product as a chiral ligand for asymmetric catalysis is also demonstrated.

5. Schedule and prospect for the future

In the following FY2021, 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 2020 List of Publications Resulting from the Use of the supercomputer

- (1) Zhenghua Li, Liang Zhang*, Masayoshi Nishiura, **Gen Luo***, Yi Luo, and **Zhaomin Hou***. Enantioselective cyanoborylation of allenes by *N*-heterocyclic carbene-copper catalysts. *ACS Catal.* **2020**, *10*, 11685–11692. (Publication date: Sep. 11, 2020; Impact Factor: 12.35)
- (2) Shao-Jie Lou, Liang Zhang, Yong Luo, Masayoshi Nishiura, **Gen Luo***, Yi Luo, and **Zhaomin Hou***. Regiodivergent C–H alkylation of quinolines with alkenes by half-sandwich rare-earth catalysts. *J. Am. Chem. Soc.* **2020**, *142*, 18128–18137. (Publication date: Sep. 28, 2020; Impact Factor: 14.612)
- (3) 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. 2, 2021; Impact Factor: 14.612)
- (4) Yanan Zhao, **Gen Luo**, Xin Xu, **Zhaomin Hou**, and Yi Luo*. Computational study of the reactivity of rare-earth/phosphorus Lewis pairs toward polymerization of conjugated polar alkenes. *Inorg. Chem. Front.* **2020**, *7*, 4600–4610. (Publication date: Oct. 6, 2020; Impact Factor: 5.958)
- (5) Jimin Yang, **Gen Luo***, Yang Yu, Jingping Qu, **Zhaomin Hou**, and Yi Luo*. Theoretical mechanistic insights into dinitrogen activation by a diniobium tetrahydride: Two-state reactivity and the role of potassium cation promoter. *Inorg. Chem.* **2020**, *59*, 4626–4633. (Publication date: March 11, 2020; Impact Factor: 4.825)
- (6) Takanori Shima, Jimin Yang, **Gen Luo**, Yi Luo*, and **Zhaomin Hou***. Dinitrogen activation and hydrogenation by C₅Me₄SiMe₃-ligated di- and trinuclear chromium hydride complexes. *J. Am. Chem. Soc.* **2020**, *142*, 9007–9016. (Publication date: Apr. 17, 2020; Impact Factor: 14.612)