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Communication

Enantioselective C−H Alkenylation of Ferrocenes with Alkynes by Half-Sandwich Scandium Catalyst

Shao-Jie Lou, Qingde Zhuo, Masayoshi Nishiura, Gen Luo,* and Zhaomin Hou*

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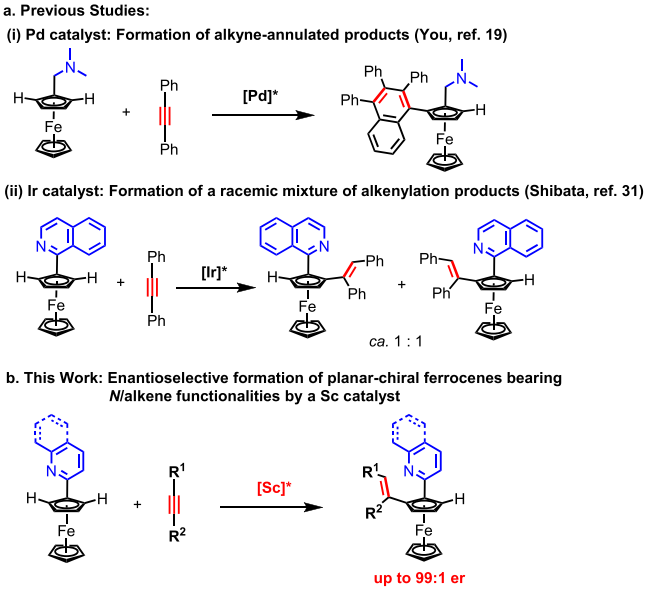
ABSTRACT: The enantioselective C−H alkenylation of ferrocenes with alkynes is, in principle, a straightforward and atom-efficient route for the construction of planar-chiral ferrocene scaffolds bearing alkene functionality but has remained scarcely explored to date. Here we report for the first time 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.

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.[1−10] 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.[5−33] In view of the high potential of chiral hybrid olefin ligands containing both a heteroatom and an olefin unit in asymmetric catalysis,[34−46] 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.[47] However, despite extensive studies and recent advances in C−H activation and transformations,[11−16] the enantioselective C−H alkenylation of ferrocenes with alkynes has remained a challenge to date because of the lack of suitable chiral catalysts. 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 (Scheme 1a, i).[19] 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 (Scheme 1a, ii) although the analogous asymmetric C−H alkylation with alkenes worked well.[31] Search for new catalysts for the asymmetric C−H alkenylation of ferrocenes with alkynes is therefore of much interest and importance.

We have recently found that half-sandwich rare-earth catalysts can serve as a unique platform for various chemical transformations,[48−70] including the enantioselective C−H addition of pyridines to alkenes,[63,65] diastereodivergent asymmetric carboamination/annulation of cyclopropenes with aminoalkenes,[66] and enantioselective construction of all-carbon quaternary stereocenters via C−H alkylation of imidazoles with 1,1-disubstituted alkenes.[70] These findings have provoked our interest in exploring the potential of rare-earth catalysts for asymmetric C−H alkenylation with alkynes.

Scheme 1. Asymmetric C−H Addition of Ferrocenes to Alkynes by Different Catalysts



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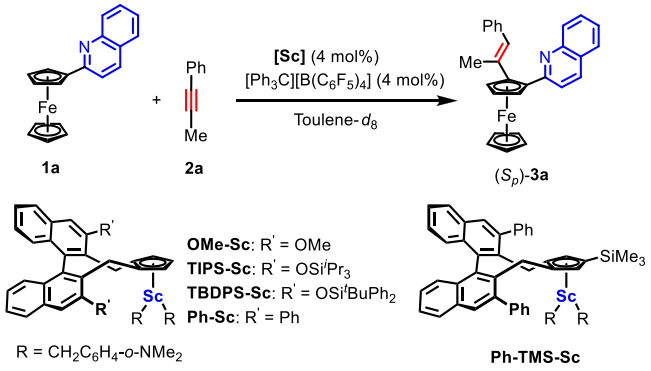
Herein, we report for the first time the enantioselective C−H alkenylation of ferrocenes with various internal alkynes by a chiral half-sandwich scandium catalyst (Scheme 1b). This protocol offers an efficient and selective route for the synthesis of a new family of planar-chiral ferrocenes bearing quinoline and pyridine/alkene functionalities with high enantioselectivity. The mechanistic details have been clarified by DFT calculations. The potential of a quinoline/alkene-functionalized ferrocene product as a chiral ancillary ligand for asymmetric rhodium catalysis is also demonstrated.

At first, we examined the reaction of a quinoline-substituted ferrocene **1a** with 1-phenyl-1-propyne **2a** by using half-sandwich scandium catalysts bearing various binaphthyl-substituted cyclopentadienyl ligands (Table 1).[71−73] The Sc

Table 1. Asymmetric C−H Alkenylation of 1a with 2a by Various Half-sandwich Scandium Catalysts[a]



entry	[Sc]	T (°C)	t (h)	yield (%)[b]	e.r.[c]
1	OMe-Sc	80	24	0	/
2	TIPS-Sc	80	24	0	/
3	TBDPS-Sc	80	24	0	/
4	Ph-Sc	80	24	61	95:5
5	Ph-TMS-Sc	80	24	81	98:2
6	Ph-TMS-Sc	70	48	61	98:2

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.07 mmol), [Sc] (4 mol %), $[Ph_3C][B(C_6F_5)_4]$ (4 mol %), toluene-d_8 (0.5 mL). [b]Yield of **3a** was determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]Enantiomer ratio of **3a** determined by HPLC analysis on a chiral stationary phase.

catalysts possessing OMe (OMe-Sc),[68] OSi(^{i}Pr)$_3$ (TIPS-Sc),[63] and OSi^{t}BuPh$_2$ (TBDPS-Sc)[63] substituents at the 3,3′-positions of the binaphthyl group in the Cp ligand, which were previously reported to show high activity and excellent enantioselectivity in the hydroarylation[63,70] and hydrosilylation[68] of alkenes, did not work in the C−H alkenylation of **1a** with **2a** under the similar conditions (Table 1, entries 1−3). In contrast, an analogous catalyst bearing phenyl substituents at the binaphthyl group (Ph-Sc)[66] afforded the desired C−H alkenylation product **3a** in 61% yield with an enantiomer ratio of 95:5 (Table 1, entry 4). The introduction of a bulky SiMe$_3$ substituent to the Cp ring of the catalyst (Ph-TMS-Sc, Figure 1)[74] gave a further higher yield (81%) and higher enantioselectivity (98:2 e.r.) (Table 1, entry 5).[75−81] Lowering the reaction temperature from 80 to 70 °C did not influence the enantioselectivity, while a lower yield of **3a** was observed (Table 1, entry 6). The formation of **3a** in the reaction of **1a** with **2a** represents the first example of enantioselective C−H alkenylation of a ferrocene compound with an alkyne, standing

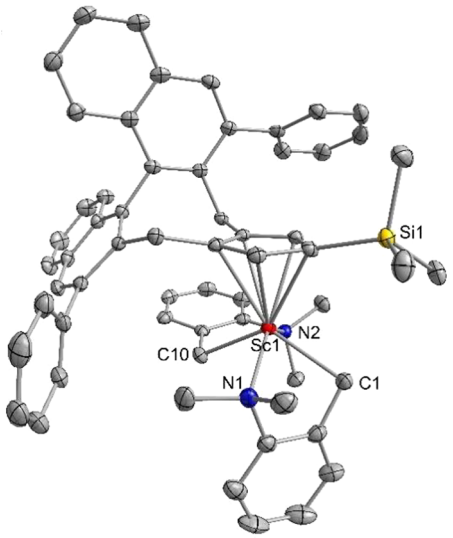


Figure 1. ORTEP drawing of Ph-TMS-Sc showing thermal ellipsoids at the 30% probability level. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Sc1−Cp (av.) 2.538(3), Sc1−C1 2.304(4), Sc1−C10 2.281(4), Sc1−N1 2.420(3), Sc1−N2 2.464(3); C1−Sc1−N1 71.63(12), C1−Sc1−N2 87.03(13), C10−Sc1−N2 72.05(12).

in sharp contrast with the analogous reactions catalyzed by Pd[19] or Ir[31] catalysts, which either gave an alkyne-annulated product or did not show significant enantioselectivity (see also Scheme 1a).

Having established the optimal conditions for the asymmetric C−H alkenylation of **1a** with **2a**, we then examined the reactions of **1a** with various alkynes. Some representative results are shown in Table 2. In addition to **2a**, internal alkynes bearing various aryl and alkyl substituents could generally serve as efficient alkenylating reagents for **1a** in the presence of Ph-TMS-Sc. The C−C bond formation took place regioselectively at the carbon atom of a C≡C unit bearing the alkyl substituent, affording the corresponding alkenylated ferrocene derivatives in high yields and excellent enantioselectivities (e.r. = 96:4−99:1). Phenyl (**3e**), naphthyl (**3f**), phenoxy (**3g**), trimethylsilyl (**3h**), chloro (**3i**, **3k**), bromo (**3j**), methylthio (**3l**), carbazolyl (**3m**), and vinyl (**3o**) functional groups in the alkyne substrates were all compatible with the catalyst, without showing erosion of the enantioselectivity. Thiophenyl (**3n**), PhS (**3q**), and ^{i}PrS (**3r**) groups directly bonded to the C≡C unit of the alkyne substrates did not hamper the reaction. The sterically demanding diphenylacetylene (**3p**) also worked well for the alkenylation of **1a**.[82] The absolute configuration of the alkenylation product **3p** was assigned to be S_p by spectroscopic comparison with a reference compound (R_p)-**3p** prepared from the well-known Ugi's amine (see the Supporting Information for details).[83]

Table 3 shows the Ph-TMS-Sc catalyzed enantioselective C−H alkenylation of various *N*-heterocycle-substituted ferrocenes with alkynes. Methyl (**3s**), bromo (**3t**), and fluoro (**3u**) substituents at the quinoline moiety of the ferrocene substrates did not hamper the enantioselectivity (e.r. = 96:4−98:2). A fused polycyclic quinoline unit (**3v**) was well accommodated. *n*-Butyl (**3w**) or bromo (**3x**) substituent at a Cp ring of the ferrocenes was also compatible with the C−H alkenylation at the other Cp ring, without deteriorating the enantioselectivity. In addition to quinoline substituents,

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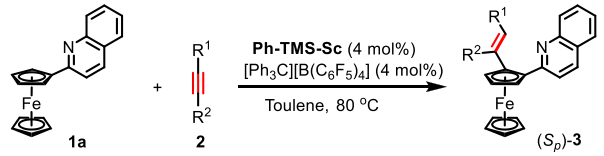
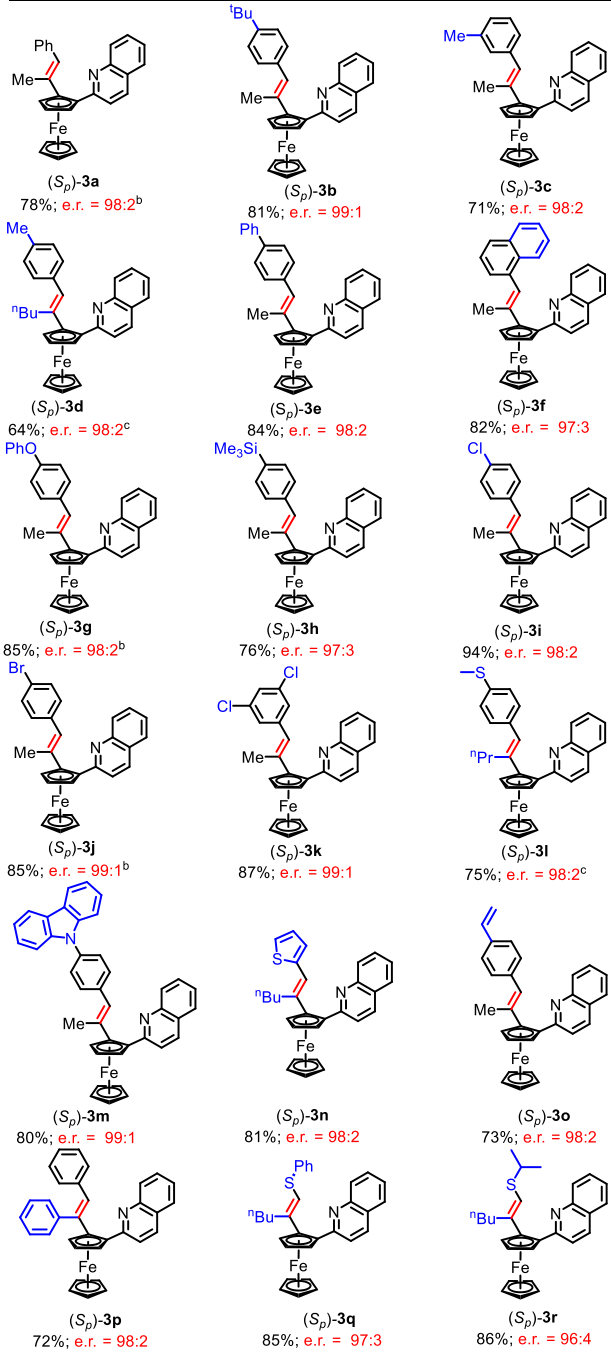
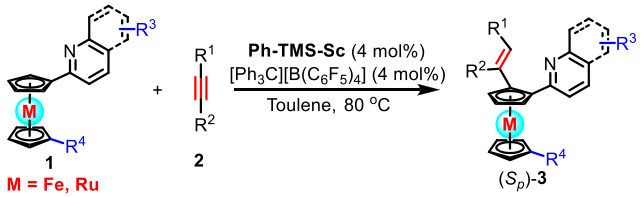
Table 2. Asymmetric C−H Alkenylation of 1a with Various Alkynes by Ph-TMS-Sc[a]

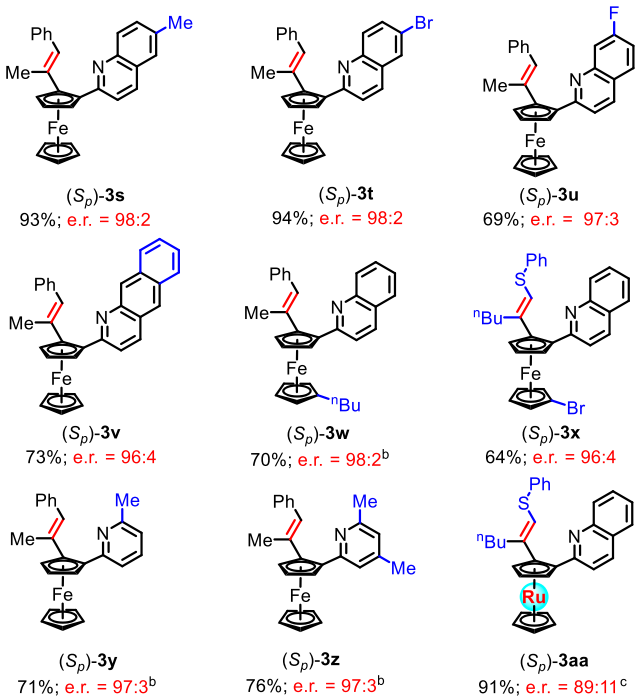




[a]Reaction conditions unless noted otherwise: **1a** (0.05 mmol), **2** (0.07 mmol), Ph-TMS-Sc (4 mol %), $[Ph_3C][B(C_6F_5)_4]$ (4 mol %), toluene (0.5 mL), 80 °C, 24−72 h, isolated yield, r.r. > 20:1, e.r. determined by HPLC analysis on a chiral stationary phase. [b]**1a** (0.20 mmol), **2** (0.30 mmol), Ph-TMS-Sc (4 mol %), $[Ph_3C][B(C_6F_5)_4]$ (4 mol %), toluene (2.0 mL), 80 °C, 48 h. [c]Ph-TMS-Sc (8 mol %), $[Ph_3C][B(C_6F_5)_4]$ (8 mol %).

Table 3. Asymmetric C−H Alkenylation of Various *N*-Heterocycle-Substituted Ferrocenes and Ruthenocene with Alkynes by Ph-TMS-Sc[a]





[a]Reaction conditions unless noted otherwise: **1** (0.05 mmol), **2** (0.07 mmol), Ph-TMS-Sc (4 mol %), $[Ph_3C][B(C_6F_5)_4]$ (4 mol %), toluene (0.5 mL), 80 °C, 24−72 h, isolated yield, r.r. > 20:1, e.r. determined by HPLC analysis on a chiral stationary phase. [b]Ph-TMS-Sc (8 mol %), $[Ph_3C][B(C_6F_5)_4]$ (8 mol %). [c]23 °C, 24 h.

pyridine-substituted ferrocenes were also suitable for the present C−H alkenylation reaction, efficiently yielding the corresponding pyridine/alkene-functionalized planar-chiral ferrocene derivatives (**3y**, **3z**) in excellent enantioselectivity (e.r. = 97:3).[84] Besides ferrocenes, a ruthenocene substrate could also be efficiently C−H alkenylated in an enantioselective fashion (**3aa**).

To gain insights into the C−H bond cleavage step of a quinoline-functionalized ferrocene compound **1a**, we carried out several deuterium-labeling experiments (Scheme 2). When 2-ferrocenyl-8-deuterium-quinoline (**1a−d$_1$**) was stirred with Ph-TMS-Sc (4 mol %) and $[Ph_3C][B(C_6F_5)_4]$ (4 mol %) in toluene at 80 °C for 8 h, a D/H scrambled product **1a-d/h** was formed (Scheme 2a). This suggests that the C−H activation of **1a** by the scandium catalyst could take place at both the C8 position of the quinoline substituent and the *ortho*-positions of the Cp group in the ferrocene moiety, similar to what was observed previously in the case of 2-phenylquinoline.[62] When the reaction of **1a−d$_1$** with **2a** was carried out in the presence of Ph-TMS-Sc/$[Ph_3C][B(C_6F_5)_4]$ at 80 °C for 48 h, the ferrocene C−H alkenylation product (S_p)-**3a−d** was formed accompanied by the similar H/D scrambling (Scheme 2b).

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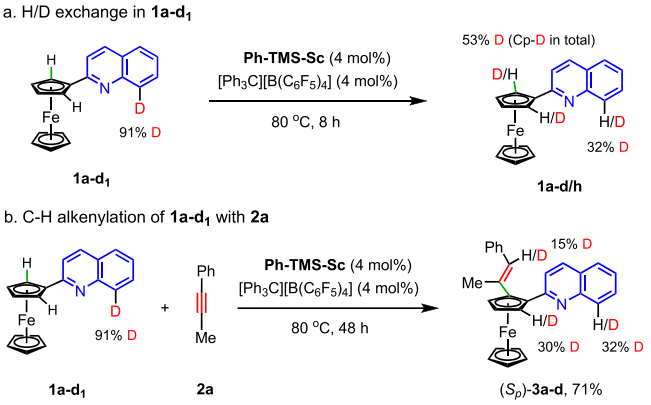
Scheme 2. Deuterium-Labeling Experiments



These results suggest that the alkyne insertion reaction could occur regio- and enantioselectively at a ferrocene C−H position, although C−H activation at the C8 position of the quinoline unit may also take place.

To gain more information on the reaction mechanism, we performed the density functional theory (DFT) calculations (see Supporting Information for details). 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, see also Figures S14−S16). 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).[85] 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

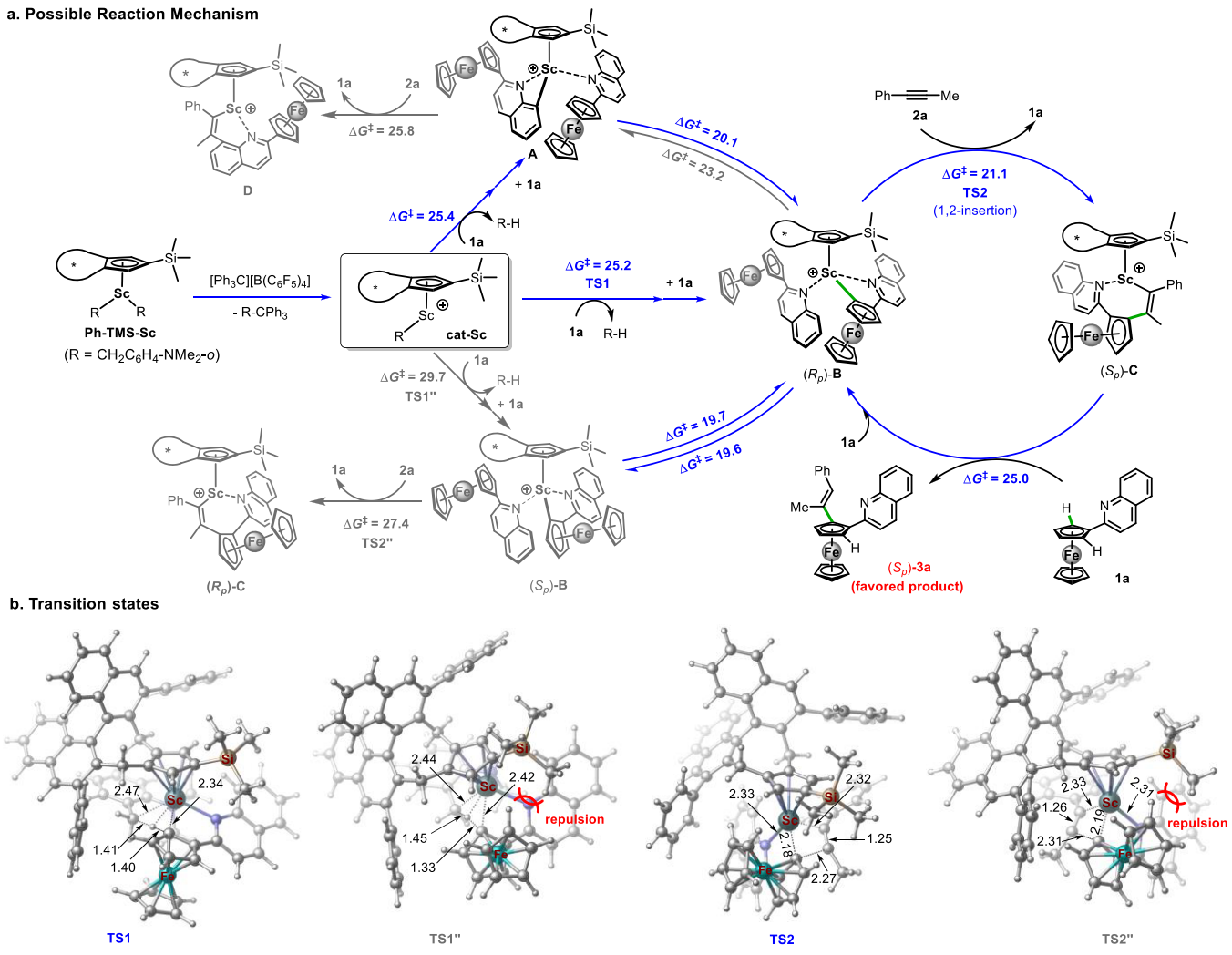


Figure 2. Possible mechanism of enantioselective C−H alkenylation of **1a** with **2a** by Ph-TMS-Sc. The free energy barriers ($\Delta G^{\ddagger}$) in solution are given in kcal/mol. Bond distances are given in angstrom (Å). The energy values were obtained at the M06/6-311+G(d,p)&SDD (SMD, toluene)//B3PW91/6-31G(d)&SDD (353.15 K) level of theory (see the Supporting Information for more details).

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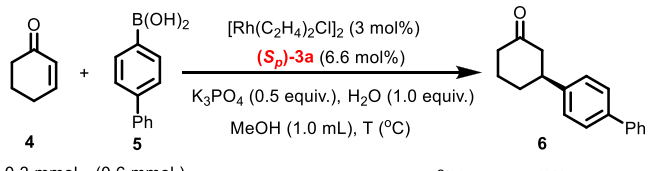
cat-Sc with **1a** requires a much higher energy barrier (via TS1″, $\Delta G^{\ddagger}$ = 29.7 kcal/mol). Although (S_p)-**B** could be alternatively generated from (R_p)-**B** ($\Delta G^{\ddagger}$ = 19.6 kcal/mol), the alkyne insertion into (S_p)-**B** to give (R_p)-**C** (via TS2″, $\Delta G^{\ddagger}$ = 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).

To probe the potential of the *N*/alkene-functionalized ferrocene products obtained in this work as chiral ligands in asymmetric catalysis, we examined (S_p)-**3a** in the Rh-catalyzed 1,4-addition of an arylboronic acid **5** to an α,β-unsaturated ketone **4** (Scheme 3).[86] The desired β-arylated ketone product

Scheme 3. Using (S_p)-3a as a Chiral Ligand in Rh-Catalyzed Asymmetric Transformation



T (°C)	Yield (%)	e.r.
40	92	93:7
r.t.	62	96:4

6 was obtained in a decent yield with a high-level of enantioselectivity under mild conditions (e.r. = 96:4 at room temperature), demonstrating that the *N*/alkene-functionalized planar-chiral ferrocenes can serve as excellent ancillary ligands in asymmetric catalysis.[39]

In summary, by using a newly prepared chiral half-sandwich scandium catalyst Ph-TMS-Sc, we have achieved for the first time the enantioselective C−H alkenylation of ferrocenes with diverse internal alkynes. This protocol offers a straightforward route for the synthesis of a new family of *N*/alkene-functionalized planar-chiral ferrocenes with high enantioselectivity, high yields, broad substrate scope, and 100% atom efficiency. Deuterium-labeling and computational studies have revealed that although C−H activation at both the ferrocene Cp unit and the C8 position of the quinoline moiety in a quinoline-substituted ferrocene compound such as **1a** is possible, the alkenylation with an alkyne such as **2a** favors the Cp unit in an enantioselective fashion. The successful use of (S_p)-**3a** as a chiral ligand in the Rh-catalyzed asymmetric 1,4-addition of an aryl boric acid to cyclohexanone demonstrates the high potential of the *N*/alkene-functionalized planar-chiral ferrocene products obtained in this work in asymmetric catalysis. Further studies on rare-earth-catalyzed asymmetric C−H functionalization and related transformations are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13166.

Detailed experimental procedures, computational details, spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1995887 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Gen Luo − *Institutes of Physical Science and Information Technology, Anhui University, Hefei 230601, China;* orcid.org/0000-0002-5297-6756; Email: luogen@ahu.edu.cn

Zhaomin Hou − *Advanced Catalysis Research Group, RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan; Organometallic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, Wako, Saitama 351-0198, Japan;* orcid.org/0000-0003-2841-5120; Email: houz@riken.jp

Authors

Shao-Jie Lou − *Advanced Catalysis Research Group, RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan;* orcid.org/0000-0003-3700-6812

Qingde Zhuo − *Organometallic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, Wako, Saitama 351-0198, Japan*

Masayoshi Nishiura − *Advanced Catalysis Research Group, RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan; Organometallic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, Wako, Saitama 351-0198, Japan;* orcid.org/0000-0003-2748-9814

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c13166

Notes

The authors declare no competing financial interest.

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