Secondary Cationic Interaction Driven Substrate Ligand Affinity for Pd^{II}-Catalyzed Enantioselective C-H Activation of Ferrocenyl Amines

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KEYWORDS: Ferrocene; Enantioselective C-H Activation; Ligand Acceleration; Annulation; Palladium Catalysis; Secondary Interaction

ABSTRACT: Secondary amines as a directing group for C-H activation have limitations as they are prone to undergo oxidation, allylic deamination, and *β*-hydride elimination. The fundamental challenge observed here is the competition between the desired C-H activation versus the vulnerable *β*-C-H bond of secondary amine when the substrate ligand affinity is not strong enough. Herein, a potential of axially chiral NOBINAc ligand is revealed to accelerate the enantioselective Pd^{II}-catalyzed C-H activation process of ferrocenyl secondary amines. Further, the secondary interaction of cesium cation with NOBINAc ligand and sulfonate group of secondary amine plays an impressive role in mitigating the potential threat of *β*-hydride elimination *via* an enhanced substrate ligand affinity. This approach resulted in enantioselective C-H activation, intermolecular annulation, and alkenylation of ferrocenyl secondary amines with allenes and activated olefines, leading to ferrocene fused tetrahydropyridines and alkenylated ferrocenyl amines with up to 70% yields and 99:1 *er*.

The journey of ferrocene began in the 1950s, and it quickly garnered attention due to its outstanding electronic and structural characteristics.[1,2] It features a highly reversible one-electron redox event and the intriguing ability to exhibit planar chirality, positioning it as an esteemed framework for asymmetric transformations in academia, industry,[2a] material chemistry,[2b] and medicinal chemistry.[2c] In the last few decades, ferrocene has evolved into one of the most extensively researched and developed systems for synthesizing planar chiral molecules. Especially the notable contribution of ferrocene-fused *N*-heterocycles in various asymmetric organic transformations (Figure 1).[3] Previous methodologies for the synthesis of chiral ferrocene fused *N*-heterocycle molecules demand conventional multi-step synthetic routes[3a] or intramolecular transition-metal catalyzed annulation process. However, only pre-designed tethered directing groups were capable of oxidative addition and cyclo-oligomerization for performing the subsequent annulation.[4] Recently, transition metal-catalyzed intermolecular annulation has been developed to reduce methodological complexity. However, the current techniques for accomplishing highly enantioselective ferrocene fused ring synthesis are quite limited and require challenging multi-steps for the synthesis of highly specific ligands to achieve high enantioselectivity in the rigid amide directing groups.[5]

Pd^{II} / Pd^{II} or Pd^{II} / Pd^{0} metal catalysis offers a more accessible approach for highly enantioselective C-H activation/annulation.[6] Therefore various ligands have been developed for Pd^{II}-catalysis, solving various fundamental challenges associated with enantioselective C-H activations.[7-8]

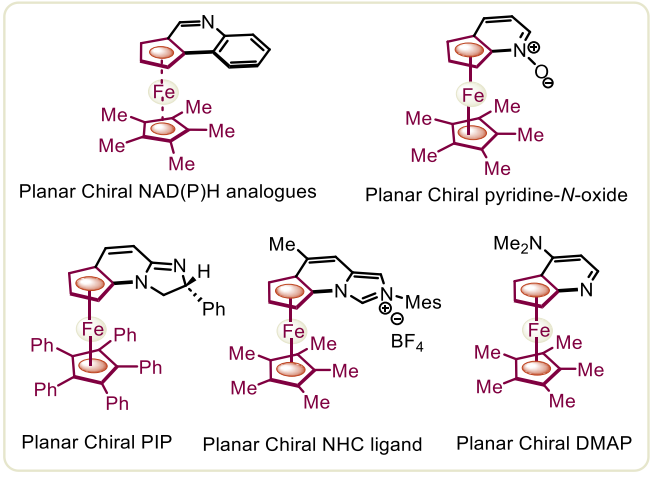
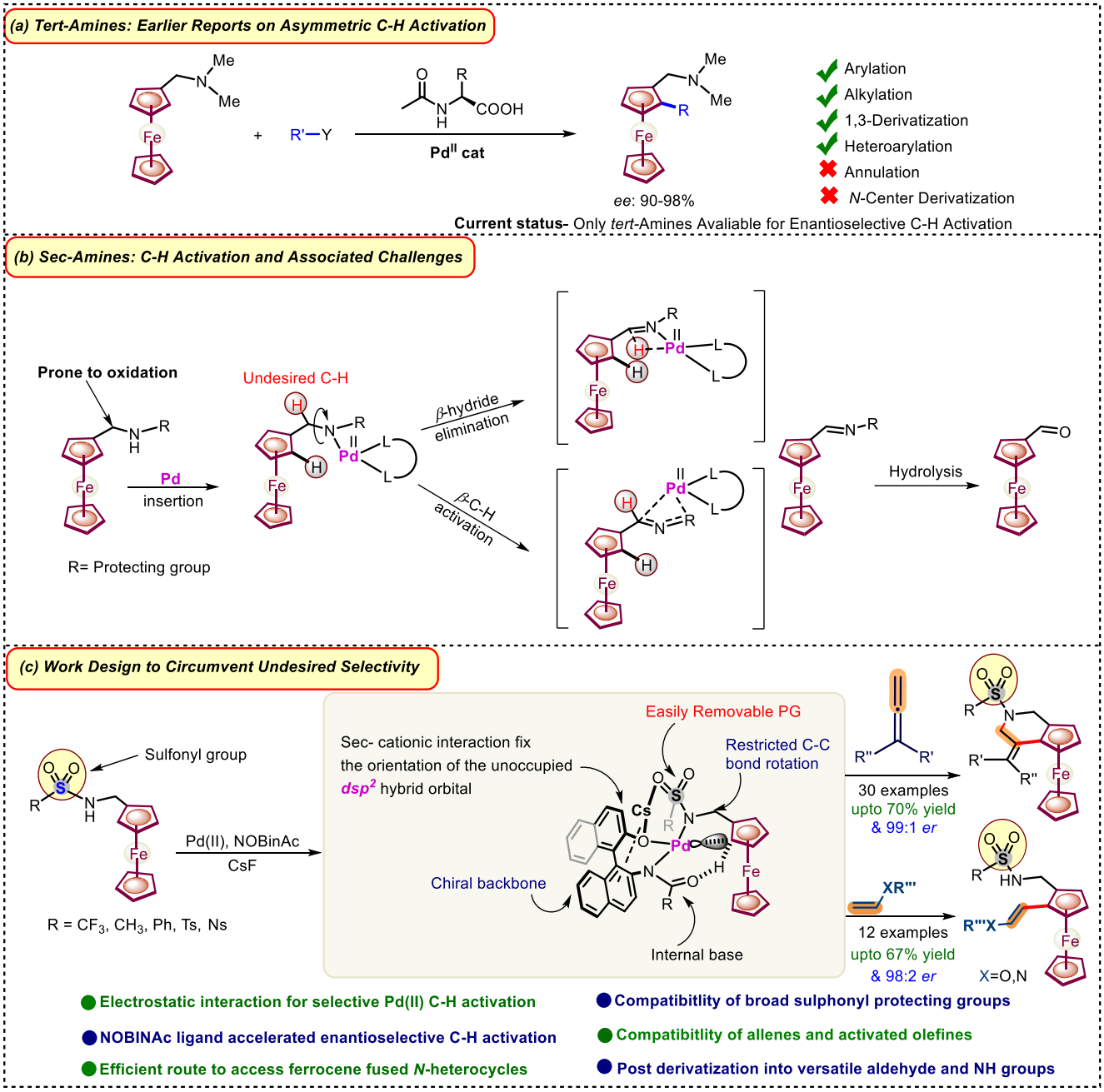


Figure 1. Application of Ferrocene Fused *N*-Heterocycles

Scheme 1. Previous Development on TM-Catalyzed Enantioselective C-H Functionalization on Ferrocene and Rational Design for Enabling Secondary Amines as a Directing Group for Annulation

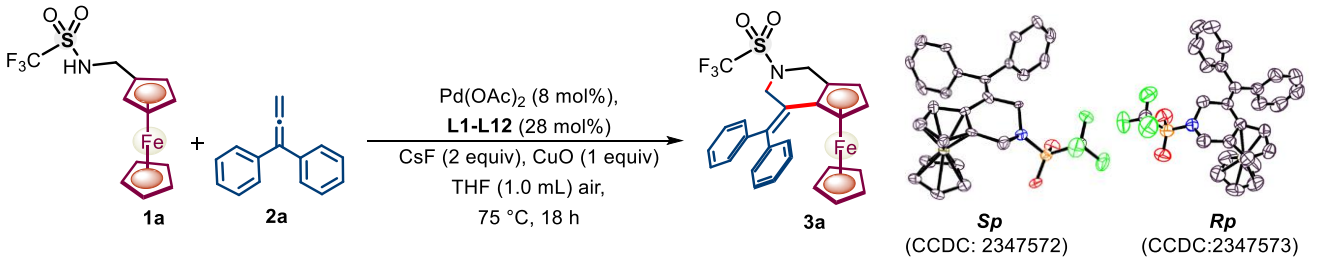


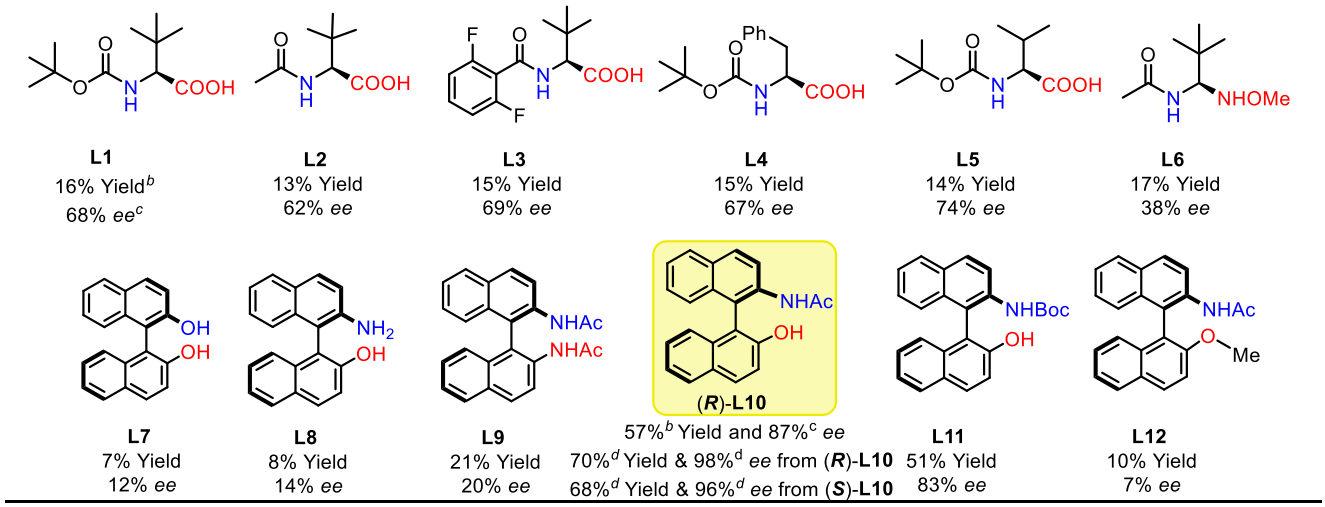
Here, the ligand plays a crucial role in regulating the selectivity and expediting the C-H activation process.[9] In certain instances, additional secondary interactions within the directing group and ligands generate the ideal catalytic pocket for C-H activation by fixing the orientation of vacant Pd^{II} dsp^2-hybrid orbital within a square planar geometry.[10] Additionally, it also helps to dictate chirality in certain cases.[11] The organometallic ferrocene has met with limited success in this regard; only *tert*-amine is presently available for enabling highly enantioselective C-H activation[12] (Scheme 1a). *tert*-Amine-directed Pd^{II} catalyzed C-H activation enables arylation,[12b] alkylation,[12c] 1,3-derivatization,[12d] and C-H heteroarylation.[12e-12g] However, a subsequent annulation process is not possible despite the nature of highly enantioselective C-H activation (Scheme 1a). Thus, the development of enantioselective C-H activation in ferrocenyl secondary amines is highly desirable, which could also eliminate the tedious task of demethylation from the NMe_2 directing group for further derivatization.[13] Prior instances of employing secondary amines as directing groups shown a propensity for either undergoing oxidation, allylic deamination, β-hydride elimination, and formation of inactive *bis*-amine Pd^{II} complexes (Scheme 1b).[14]

Our group has been working on the C-H activation of ferrocene. Recently, we embarked on enantioselective C-H activation strategies and preparation of chiral ferrocene molecules from ferroceneamides.[15] Further, we were curious to investigate the diverse possibilities offered by the ferrocenyl secondary amines for the development of catalytic enantioselective C-H activation. The secondary amines are difficult directing groups for C-H activation/functionalization by TM-catalysed (*vide supra*) and conventional *ortho*-lithiation routes.[16] Consequently, C-H activation/functionalization in ferrocenyl secondary amines has not been studied to date; nonetheless, secondary amines offer numerous opportunities for further transformations. Here, we present secondary interaction-driven NOBINAc ligand accelerated Pd^{II}-catalyzed enantioselective C-H activation of ferrocenyl secondary amines. Further, a range of easily removable *N*-sulfonyl groups consisting of ferrocenyl secondary amines with different allene and activated alkene coupling partners has been explored for the annulation and alkenylation to synthesized chiral ferrocene-fused pyridine and 1,2-alkenylated amine derivatives showing 70% yield and up to 99:1 *er*. The control experiments and DFT calculations have been carried out to shed light on the role of secondary cationic interaction on NOBINAc ligand accelerated Pd-catalyzed C-H activation.

We initiated our study with ferrocenyl-*secondary-amine* **1a** to explore the enantioselective C-H activation by using $Pd(OAc)_2$ catalyst, chiral ligand, and CuO oxidant in the presence of an additive CsF in THF (Scheme 2, SI, Tables S1-S5). Fascinated by the distinct regio-, chemo-, divergent one to three carbon synthons possibility, and further functionalization opportunity offered by allenes,[17] we set to explore allenes (**2a-2j**) as a coupling partner for enantioselective C-H activation followed by annulation reaction. Initially, mono-protected amino acid (MPAA) ligands were tried for enantioselective C-H activation of ferrocenyl-*sec-amine* **1a** with allene **2a**. Monoanionic (L-X) MPAA ligands **L1-L5** led to poor yield (13-16%) of annulated ferrocene fused tetrahydropyridine **3a** along with moderate 62-74% enantioselectivity (Scheme 2). Ligand **L5** yielded the best results among ligands **L1-L5**, achieving a 14% yield and moderate 87:13 *er* (Scheme 2). Meanwhile, di-anionic (X-X) derivatized MPAA **L6** yielded 17% of **3a** with a significant loss in enantioselectivity (38% *ee*). Furthermore, in the presence of MPAA ligands (**L1-L6**), the excessive formation of a side product, ferrocene carboxaldehyde, was observed in the reaction, presumably due to the background oxidation and β-hydride elimination from the ferrocenyl-*sec-amine* **1a** by its undesired interaction with the Pd^{II} catalyst.[18]

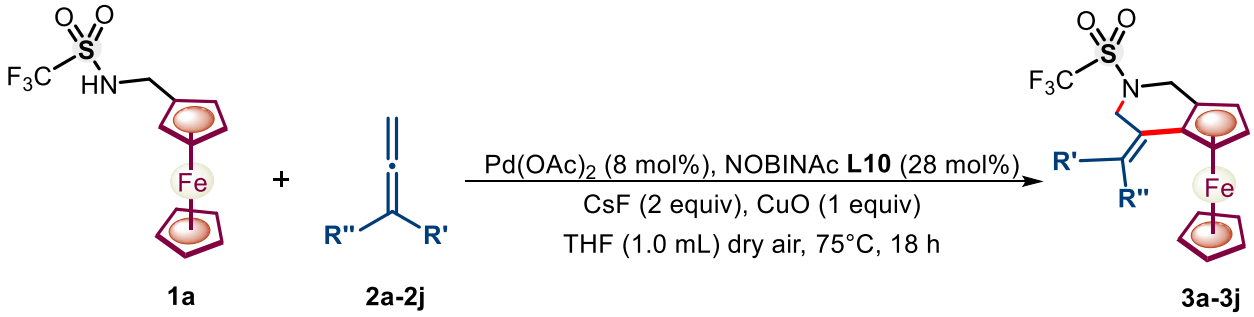
Scheme 2. Screening of Ligand and Optimization of the Reaction Conditions





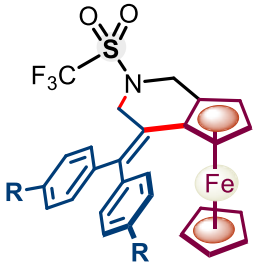
[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.004 mmol), Ligand (0.014 mmol), CsF (0.1 mmol), CuO (0.05 mmol), THF (1ml), air, T °C, 18 h. [b] Crude yield of **3a** is determined by ^1H NMR with CH_2Br_2 as an internal standard. [c] *ee* of **3a** was determined by HPLC analysis. [d] Isolated yield of **3a** and enantioselectivity when reaction carried out under dry air.

Scheme 3. Substrate Scope of Allenes Derivatization[a]

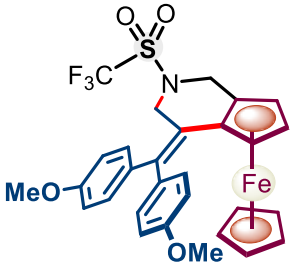


1a **2a-2j** **3a-3j**

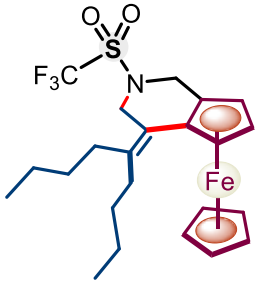
Allene Derivatization



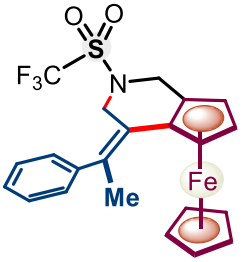
(R_P)-**3a**, R = H (70%); 99:1 *er*[b]
(S_P)-**3a**, R = H (68%); 96:4 *er*[c]
(R_P)-**3b**, R = Me (65%); 97:3 *er*
(S_P)-**3b**, R = Me (62%); 98:2 *er*[c]
3c, R = F (68%); 95:5 *er*



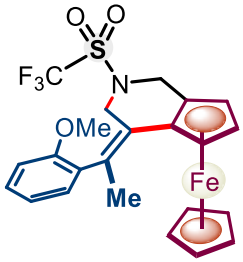
3d (62%), 96.5:5 *er*



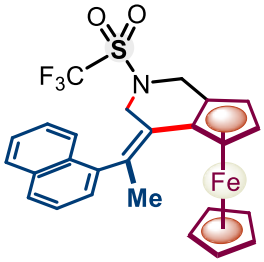
3e (59%), 89:11 *er*



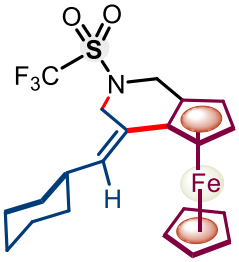
3f (63%), 97:3 er; E:Z;1:10[d]



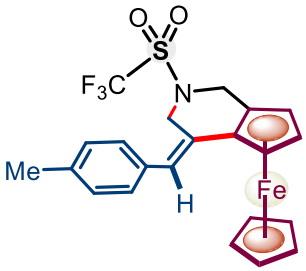
3g (55%), 97:3 *er*; *E:Z*;1:1.5



3h (60%), 98.5:1.5 *er* *E:Z*;1:10



3i (56%), 86:14% *er;* *E* : *Z*; 1:5

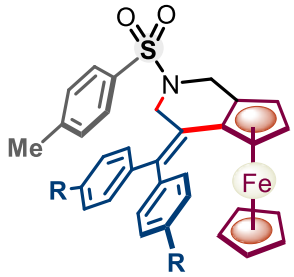


3j (50%), 95.5:4.5 *er;* *E* : *Z*; 1:2

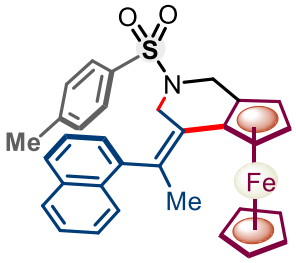
[a] Isolated yields of **3a-3j,** the product was obtained by using (*R*)-NOBINAc otherwise stated. [b] *er* of the product was determined using an HPLC analysis. [c] *er* of the product obtained by using (*S*)-NOBINAc. [d] *E:Z* was determined by ^{1}H NMR.

Interestingly, during screening of axially chiral binaphthyl-derived ligands **L7-L10**, NOBINAc ligand **L10**, which was recently developed by Gulias and Mascarenas *et al.*,[8e] offered a good 87% *ee* and moderate yield (57%) of ferrocene fused tetrahydropyridine **3a**. Further, screening of reaction conditions by modifying the NOBINAc to *N*-Boc group **L11** and NOBINAc to -OMe group **L12** afforded enantioselectivity 83 and 7% *ee* with low 51 and 10% yields, respectively. To our delight, NOBINAc ligand **L10**, under dry air atmospheric conditions, offered a 70% yield with an excellent 99:1 *er* of **3a** (see SI, Tables S1-S5). Moreover, using *S*-NOBINAc **L10** afforded opposite enantiomer (*Sp*)-**3a** in nearly the same yield and *er*. The absolute configuration of both the enantiomers of **3a** and their structures have been studied by single crystal XRD (Scheme 2). After the optimization of the reaction conditions, the applicability of the developed reaction methodology was explored with regard to a variety of allenes (Scheme 3). *α,α*-Diaryl substituted symmetrical allenes **2b-2d** with electron-donating and withdrawing substituents reacted smoothly under NOBINAc **L10**-accelerated reaction conditions, leading chiral tetrahydropyridines **3b-3d** in 62-68% yields and 95:5-99:1 *er*. Further *α,α*-unsymmetrical allenes **2f-2j** also underwent enantioselective annulation reaction to afford respective tetrahydropyridines **3f-3j**

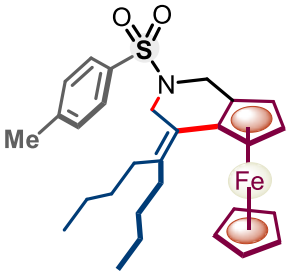
Scheme 4. Substrate Scope with Regards to Ferrocenylamines [a-c]



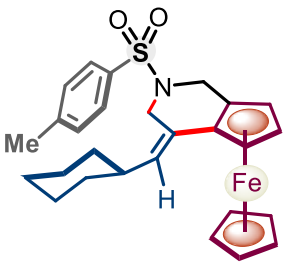
(R_P)-**3k**, R = Me (55%); 94:6 *er*
(S_P)-**3k**, R = Me (53%); 99:1 *er*
(S_P)-**3l**, R = H (58%); 95:5 *er*
(R_P)-**3l**, R = H (57%); 98:2 *er*



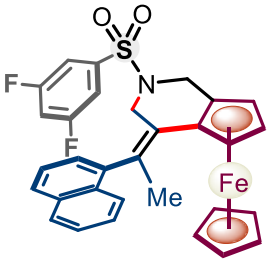
3m (53%); 96:4 *er*
E:*Z*, 1:10



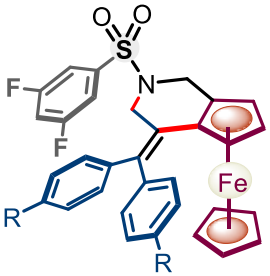
3n (56%); 92:8 *er*



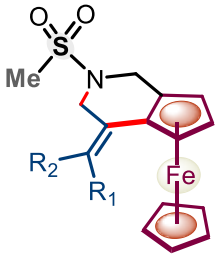
3o (53%); 97.5:2.5 *er*
E:*Z*; 1:5



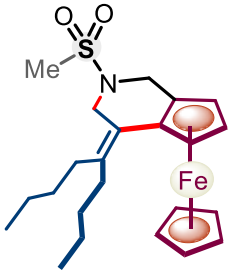
3p (47%); 94:6 *er*
E:*Z*; 1:10



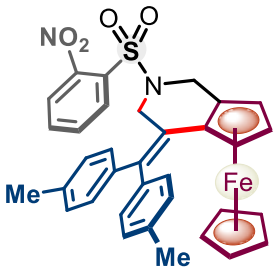
3q, R= H (45%); 93:7 *er*
3r, R= Bu (45%); 92.5:7.5 *er*
3s, R= Me (50%); 94:6 *er*



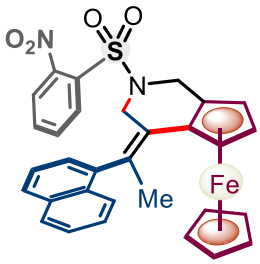
3t, R_1 = Me; R_2 = Ph (42%); 91:9 *er* *E*:*Z*; 1:10
3u, R_1 = H; R_2 = Cy (38%); 94:6 *er* *E*:*Z*; 1:4



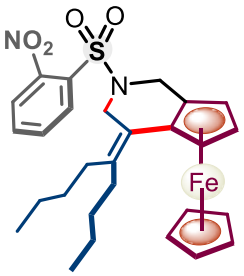
3v (35%); 86:14 *er*



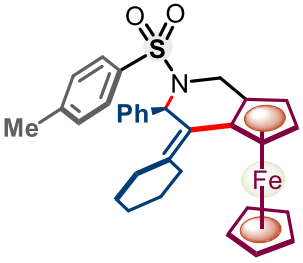
3w (28%); 97:3 *er*



3x (31%); 94:6 *er*
E:*Z*; 1:3



3y (34%); 96.5:3.5 *er*



3z, 58% yield

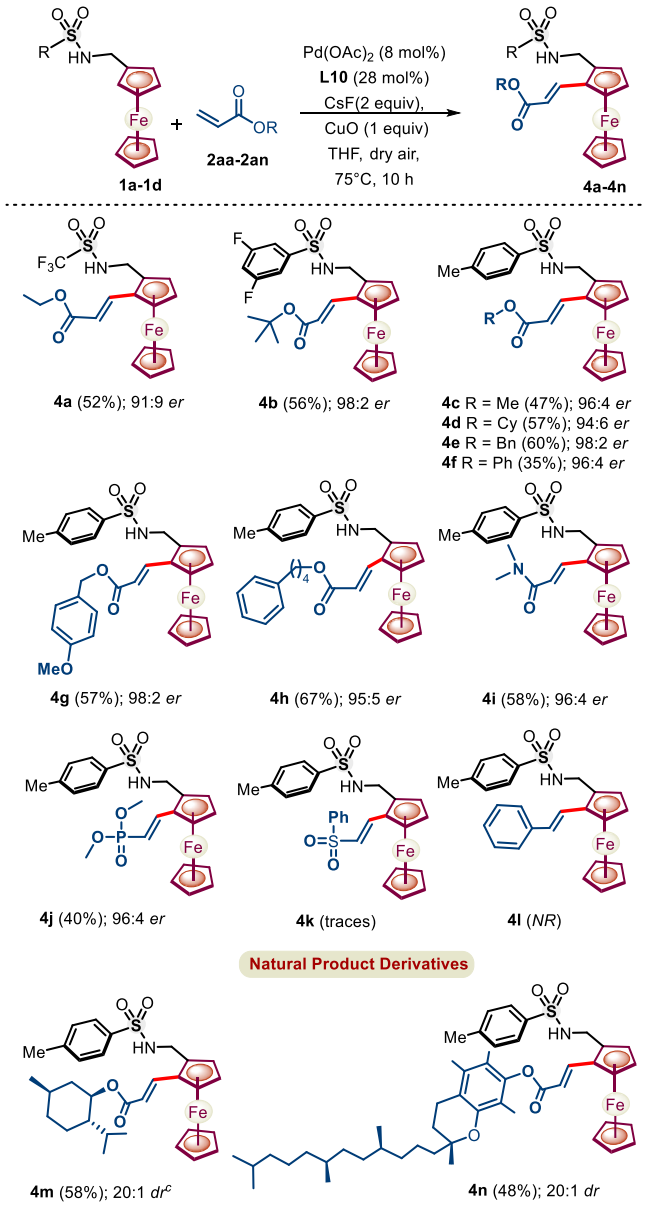
[a] Isolated yields of **3k-3z**, the product was obtained by using (*R*)-NOBINAc otherwise stated. [b] *er* of the product was determined using an HPLC analysis. [c] *er* of the product obtained by using (*S*)-NOBINAc. [d] *E*:*Z* was determined by ^{1}H NMR.

in 86:14-97.5:2.5 *er* and better *E*:*Z* selectivity up to (1:10) and (1:5). Whereas substitution at phenyl ring lowers the *E*:*Z* selectivity as phenyl-substituted tetrahydropyridines **3g** and **3j** were obtained in a poor *E*:*Z* upto 1:2. Alkyl substituted allenes **2e, 2i** offered alkyl-substituted tetrahydropyridines **3e, 3i** in nearly same yields, however, with relatively lower *er* (89:11 and 86:14 *er*). It seems the triflorosulfonyl (-NHTf) group not only facilitates the C-H activation but also helps in preventing oxidation[19] of secondary amine through secondary cationic interactions (*vide infra*). Next, various ferrocenyl-*sec*-amines **1b-1f** having the possibility of potential secondary cationic interactions under the developed NOBINAc **L10** accelerated enantioselective C-H activation have been explored (Scheme 4). To our delight, ferrocenyl-*sec*-amines **1b-1e** having methyl, *ortho*-nitrophenyl, 3,5-diflorophenyl, *para*-methyl-phenyl sulfonyl groups also underwent enantioselective C-H-annulation leading to diversely *N*-substituted chiral tetrahydropyridines **3k-3z** ranging yields of 28-58% with 86:14-99:1 *er*. Whereas nosyl and SO_2CH_3 protected amines yielded ferrocene fused tetrahydropyridines **3t-3y** relatively lower yields 28-42% with 86:14-97:3 *er* (Scheme 4). *N*-Acetyl-protected ferrocenyl-*sec*-amine **1f** failed to afford any annulated ferrocene.

Further, styrene and activated olefin coupling partners, which could react through π-interaction with *in-situ* formed proposed metallacycle, were also explored under the

NOBINAc-accelerated reaction conditions (Scheme 5). Gratifyingly, ethyl acrylate underwent an enantioselective C-H activation reaction to provide dehydrogenative Heck-coupled ferrocenyl acrylate **4a** in 35% yield and 91:9 *er* under the optimized reaction conditions. Next, a series of substituted acrylates were coupled with ferrocenylamines **1c** and **1d** to afford respective chiral 1,2 alkenylated ferrocenyl amines **4b**-**4h** in 94:6-98:2 *er* under enantioselective NOBINAc accelerated reaction conditions.

Scheme 5. Substrate Scope with Regards to Olefins[c]

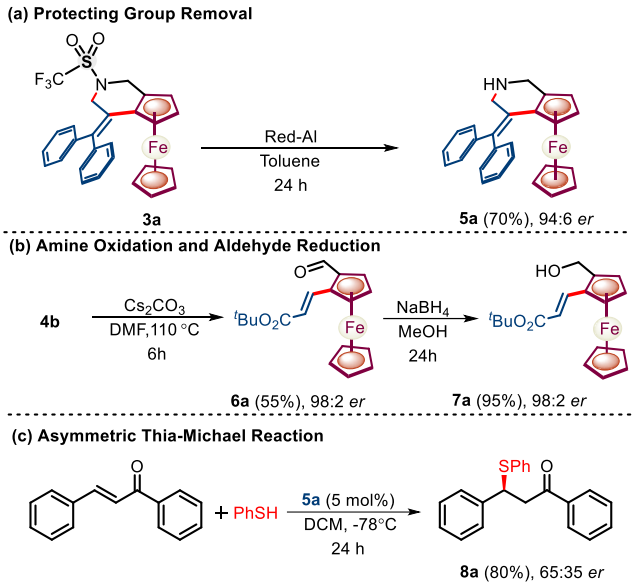


[a] Isolated yields of **4a-4n**. [b] The *ee* was determined by HPLC. [c] *dr* was determined by ^{1}HNMR

Further, not only acrylates, but also *N,N*-dimethylacrylamide, and dimethyl vinylphosphonate coupled enantioselectively with ferrocenyl amines to provide respective chiral 1,2 alkenylated ferrocenyl amines **4i**-**4j** in good 96:4 to 96:4 *er*, respectively. However, (vinylsulfonyl)benzene reacted sluggishly to afford traces of **4k** and unactivated styrene failed to react with ferrocenyl amine under the optimized reaction conditions. Next, acrylate consisting of natural moiety *L*-menthol and α-tocopherols reacted with excellent diastereoselectivity to afford natural product derivatized ferrocenyl amines in >20:1 *dr*.

Next, we have shown that the sulfonyl protection at the amine backbone can be eliminated from synthesized chiral tetrahydropyridine **3a**, affording unprotected tetrahydropyridine **5a** with a 70% yield and 94:6 *er* (Scheme 6). Further, *sec*-amine can be readily oxidized into a versatile aldehyde group leading to chiral 1,2-acrylated ferrocene carboxaldehyde **6a** in 55% yield and 98:2 *er* which has also been reduced into chiral ferrocenyl alcohol **7a** in 96% yield and 98:2 *er*. The utility of the synthesized chiral ferrocene fused amine **5a** has been tested as a catalyst for enantioselective thia-Michael reaction with chalcone providing **9a** up to 80% yield and 65:35 *er*.

Scheme 6. Post Derivatization and Application of Ferrocene fused Chiral Amine as a Catalyst

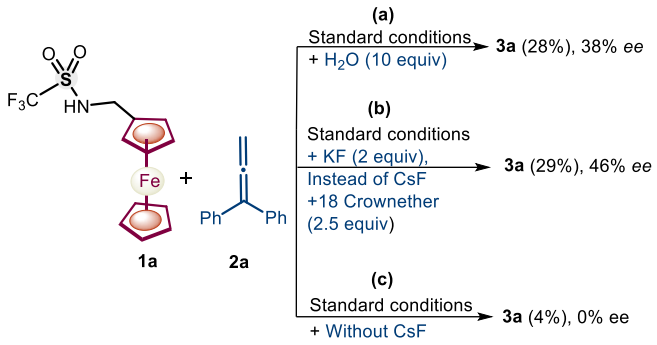


Reaction conditions: (**a**) **3a** (0.05 mmol), red Al (0.5 mmol) in dry toluene. (**b**) **4b** (0.05 mmol), Cs_2CO_3 (0.1 mmol) in DMF at 110°C for 6h. (**c**) **8a** (0.1 mmol), PhSH (0.25 mmol), **5a** (0.005 mmol).

In pursuit of an understanding of NOBINAc accelerated catalysis, control experiments were performed, where the cation from the envisioned catalytic cycle (*vide infra*) was deliberately removed using water and 18-crown ether (Scheme 7). The addition of water and 18-crown ether under the standard optimized conditions shows a significant reduction in both yield and enantioselectivity (conditions a and b, Scheme 7). On the other hand, in the absence of cation (condition c, Scheme 7), the reaction leads to only traces of annulated product **3a** without any ee. Next, ^{19}F NMR was carried out on the reaction of **1a**, $Pd(OAc)_2$, NOBINAc, and various cations (Cs_2CO_3, Na_2CO_3, and Li_2CO_3). A new peak at -76.07 ppm

corresponding to CF_3 of **1a** emerges and increases to a maximum with the increase of the size of the cations (Li^+, Na^+, and Cs^+). The only mixture of CsF and 1a does not lead to any new peak in the ^{19}F NMR. This may suggest that Cs^+ cation enhances the interaction among substrate **1a,** NOBINAc ligand **L10**, and Pd^{II} (SI, page S99). Further, the rate of the reaction in the presence and absence of NOBINAc **L10** was monitored by ^{19}F NMR with respect to **3f**, which suggests that the NOBINAc **L10** accelerates the reaction by 2.2 folds (SI, page S100).

Scheme 7. Control Experiments for Secondary Cationic Interaction on NOBINAc Catalysis



Next, the DFT computations were carried out to shed light on the influence of steric effect for high enantioselective discrimination.

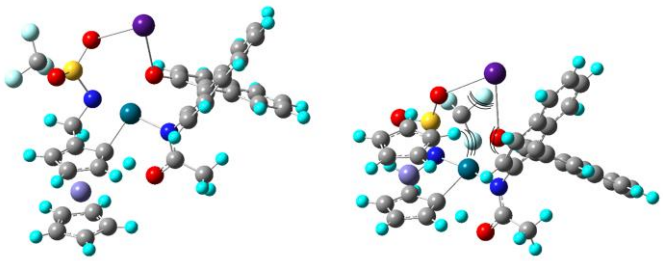
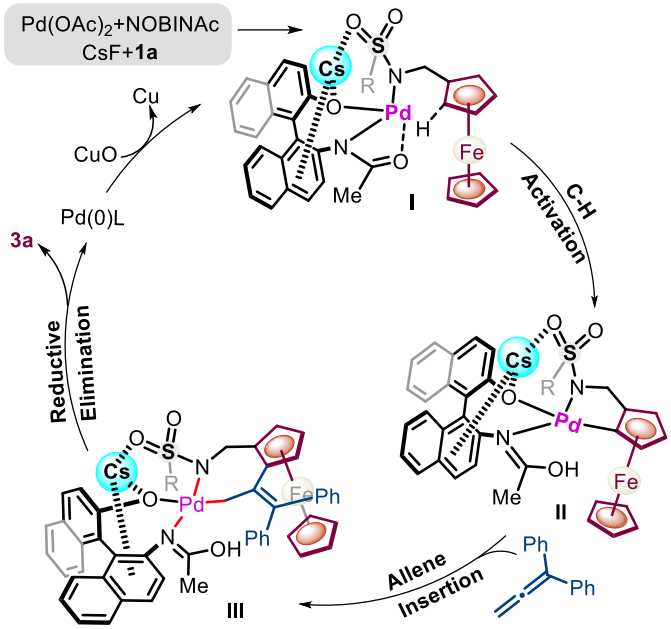


Figure 2. DFT Computation for Favorable **TS1** and Unfavorable Transition State **TS2**. [a] The optimization of the proposed structures derived from **1a**, Pd^{II}, *S*-NOBINAc, and Cs^+ and the energies were obtained at a DFT-B3LYP/LANL2DZ level of theory (for details, see SI, page S101-S108).

We were curious, whether Cs^+ ion brings binaphthyl backbone into the proximity of the Cp ring of ferrocene or Cs^+ also contributes additionally to steric discrimination with the Cp ring. The structural optimization reveals that the Cs^+ ion is away from the lower Cp ring in the favorable **TS1**, whereas, in unfavorable **TS2**, the Cs^+ ion is close to the Cp ring, leading to more steric discrimination. The relative energy difference of 2.84 kcal/mol was realized between favorable **TS1** and unfavorable **TS2** (Figure 2). In the proposed catalytic cycle (Scheme 7), the initial step seems to involve secondary cationic interaction of Cs^+ with sulfonyl group of **1a** and ligand **L10**, enabling the generation of a chiral catalytic pocket in palladium intermediate **I**. Here the cationic interaction seems to dictate vacant *dsp*²-hybrid orbital of Pd^{II} (intermediate shown in Scheme 1) towards the desired enantiotopic C-H bond and avoid interaction with *β*–C-H bond to circumvent *β*–hydride elimination. Enantiodetermining C-H activation occurs *via* the concerted metalation deprotonation (CMD) process which leads to palladacycle **II**. Subsequently, palladacycle **II** undergoes allene insertion followed by migratory insertion to form palladacycle **III**. Consequently, reductive elimination could afford ferrocene fused tetrahydropyridine **3a** with concomitant release of the catalyst.

Scheme 8. Catalytic Cycle for C-H Annulation



In summary, we have revealed a secondary cationic interaction driven NOBINAc ligand and ferrocenyl secondary amine affinity for a Pd^{II}-catalyzed highly enantioselective C-H activation and intermolecular annulation and alkenylation reactions. Furthermore, it has been observed that the secondary amines having sulfonyl group are crucial for high enantioselective induction. Consequently, a variety of sulfonyl groups (-SO_2-R) has been exploited for C-H activation. The subsequent annulation and alkenylation enable the development of an efficient methodology for synthesizing chiral ferrocene-fused tetrahydropyridine and 2-alkenylated ferrocenylamines. The sulfonyl protecting group can be effortlessly removed to provide chiral ferrocenyl secondary amine, which shows the application as a chiral catalyst. Similarly, 2-alkenylated ferrocenylamine has been oxidized into respective ferrocene carboxaldehyde which is a versatile group for further derivatization into alcohols, amines, etc. So far Initial results allowed us to explore the introduction of coupling partners within allenes and acrylates. Future investigations are underway to explore the feasibility of introducing the coupling partners through transmetallation or oxidative

addition, enabling ferrocenyl secondary amines derived arylation and heteroatom insertion reactions.

ASSOCIATED CONTENT

Supporting Information

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

X-ray crystallography data, experimental procedure, control, kinetic experiments, theoretical calculation data of **TS1** and **TS2**, characterization data, HPLC analysis and copies of ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR of the synthesized ferrocenyl amines **1a-1f**, tetrahydropyridines **3a-3z**, **4a**, and **5a** (**PDF**)

FAIR data, including the primary NMR FID files, for synthesized compounds (**ZIP**)

Accession Code

CCDC **2347572** and **2347573** contain the supplementary crystallographic data for this paper. This 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: +441223 336033.

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Author Contributions

SK and DP wrote the manuscript. DP, ADD, YDU, and RT performed synthesis and characterization. DP has performed controlled experiments. RJ and SR performed DFT computation. All authors have approved the final version of the manuscript.

Notes

The authors declare no conflict of interest.

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