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 on accelerating 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 and intermolecular annulation of ferrocenyl secondary amines with allenes, leading to ferrocene fused tetrahydropyridines up to 70% yields and 98% of *ee*.

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] Various ligands have been developed for Pd(II)-catalysis, solving various fundamental challenges associated with enantioselective C-H activations.[7-8]

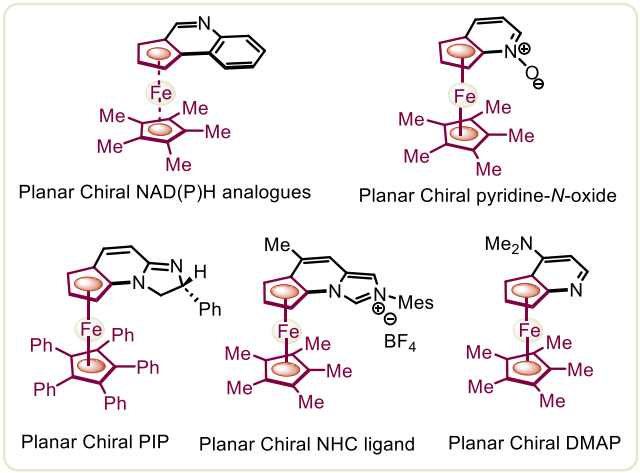
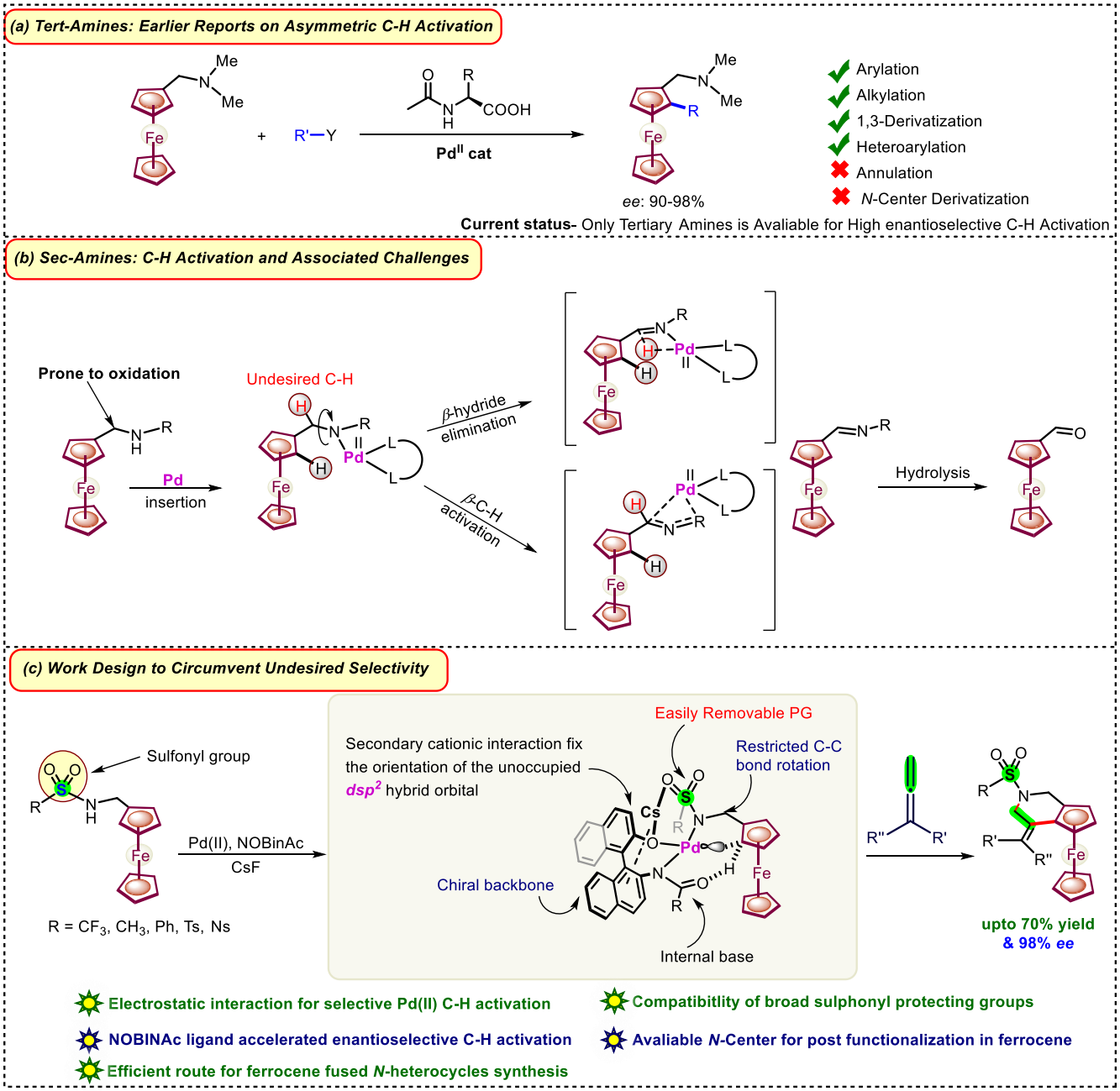


Figure 1. Application of Ferrocene Fused *N*-Heterocycles

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]

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.



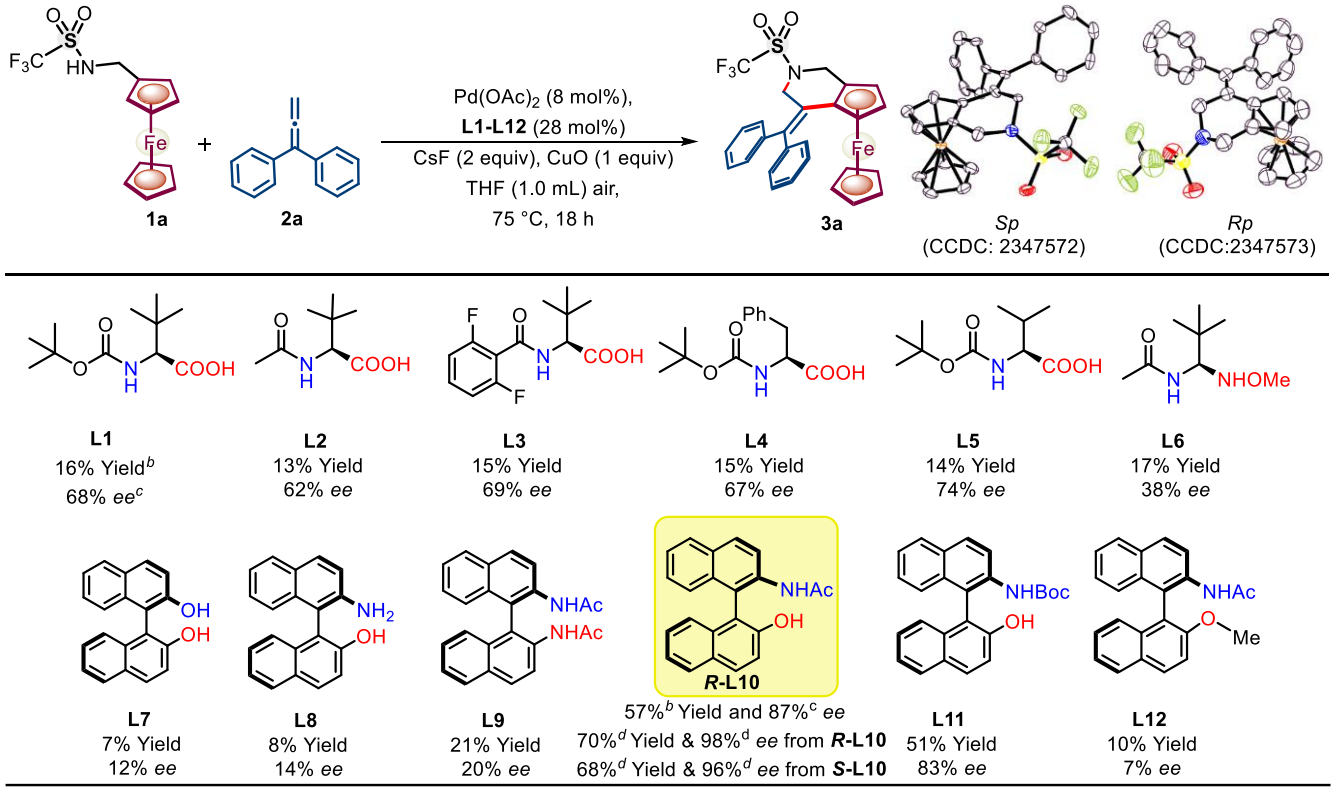
The organometallic ferrocene has met with limited success in this regard; only *tert*-amine is presently available for enabling highly enantioselective C-H activation[12] (Scheme 1a). *tert*-Amine directed Pd(II) catalyzed C-H activation enables arylation,[12b] alkylation,[12c] 1,3-derivatization,[12d] 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). 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.[15] Recently, we embarked on enantioselective C-H activation strategies and preparation of chiral ferrocene molecules from ferroceneamides. 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 allenes coupling partners has been explored for the annulation to synthesized chiral ferrocene-fused pyridine derivatives showing 70% yield and up to 98% *ee*. 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.

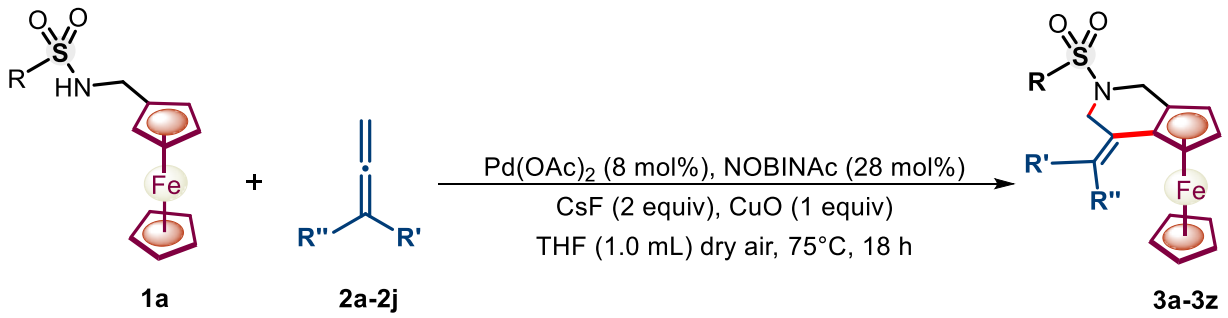
We initiated our study with ferrocenyl secondary amine **1a** to explore the enantioselective C-H activation by using $Pd(OAc)_2$ catalyst, chiral ligand, and CuO oxidant in the presence of an additive CsF in THF under air atmosphere (Scheme 2). Fascinated by the distinct regio-, chemo-, divergent one to three carbon synthons possibility, and further functionalization opportunity offered by allenes, we set to explore allenes (**2a**-**2j**) as a coupling partner for enantioselective C-H activation followed by annulation reaction.[17] Initially, mono protected amino acid (MPAA) ligands were tried for enantioselective C-H activation of ferrocenyl secondary 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 them, achieving a 14% yield and moderate 74% *ee* (Scheme 2). Meanwhile, di-anionic (X-X) derivatized MPAA **L6** yielded **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 secondary amine **1a** by its undesired interaction with the Pd(II) catalyst.[18] Interestingly, during screening of axially chiral binaphthyl-derived ligands **L7**-**L10**, NOBINAc ligand **L10**, which is 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 98% *ee* of **3a** (see SI, Tables S1-S5). Moreover, using S-NOBINAc **L10** afforded opposite enantiomer **3a** in nearly the same yield and *ee*. The absolute configuration of both the enantiomers of **3a** and their structures have been studied by single crystal XRD (Scheme 2).

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

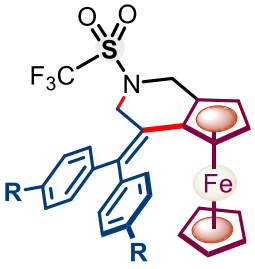


[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.00025 mmol), NOBINAc (0.01 mmol), CsF (0.075 mmol), CuO (0.025 mmol), THF (1ml), air, T °C, 18 h. [b] Crude yield of **3a** is determined by ^1H NMR with CH_2Br_2 as an internal standard. [c] *ee* of **3a** was determined by HPLC analysis. [d] Isolated yield of **3a** and enantioselectivity when reaction carried out under dry air.

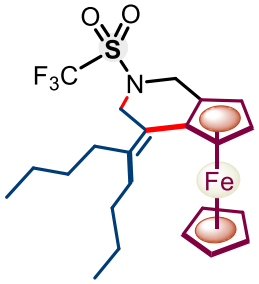
Scheme 3. Substrate Scope of Allenes Derivatization



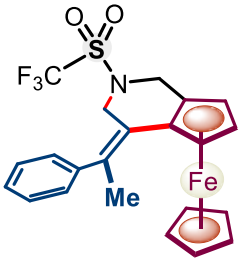
Allene Derivatization



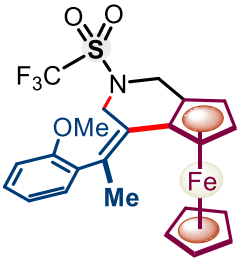
3a, R = H (70%)[b]; 99:1 *er*[c]
3b, R = Me (65%); 98:2 *er*
3c,R = F (68%); 95:5 *er*
3d,R = OMe (62%); 96.5:5 *er*



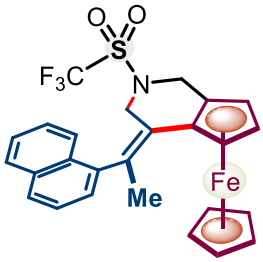
3e, 59% yield, 89:11 *er*



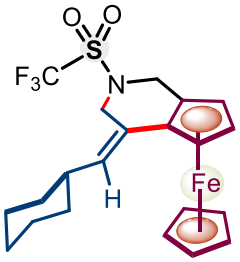
3f, 63% yield, 97:3 *er*; *E:Z*;1:10[d]



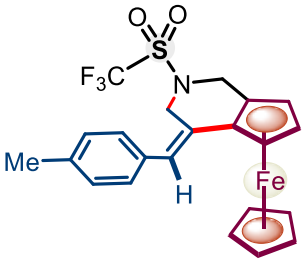
3g, 55% yield, 97:3 *er*; *E:Z*;1:1.5



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



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



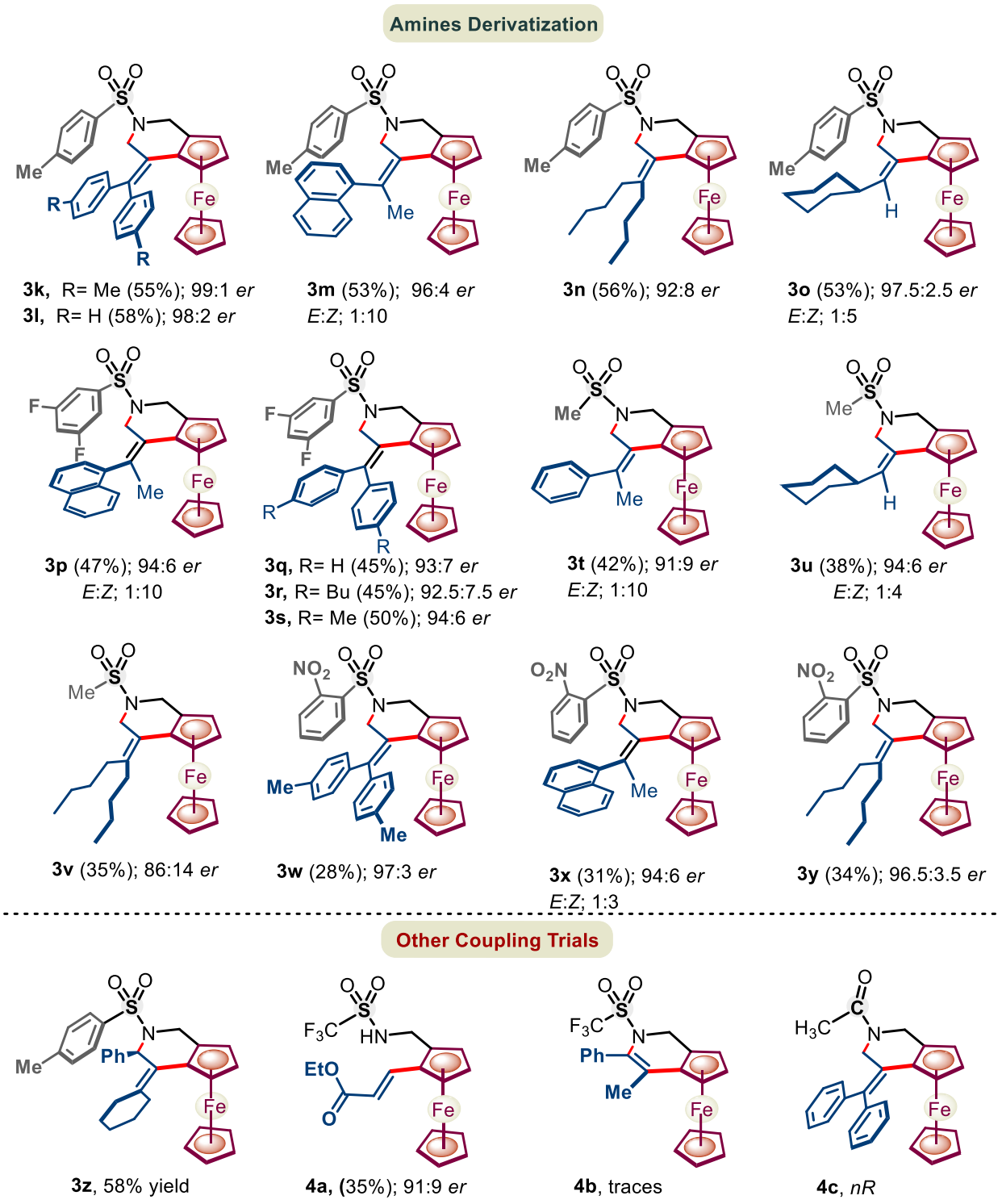
3j, 50% yield, 95.5:4.5 *er;* *E* : *Z*; 1:2

Reaction conditions: (a) **1a** (0.14 mmol), **2a** (0.28 mmol), $Pd(OAc)_2$ (0.0112 mmol), NOBINAc (0.039 mmol), CsF (0.28 mmol), CuO (0.14 mmol) THF (1 mL), dry air, 75°C, 18 h. (b) The isolated yield of the product was determined by column purification. (c) The *ee* of the product was determined using an HPLC analysis. (d) *E:Z* was determined by ^{1}H NMR Analysis.

After the optimization of the reaction conditions, the applicability of the developed reaction methodology with regard to a variety of allenes was explored (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 90-99% *ee*. Further *α,α*-unsymmetrical allenes **2f-2j** also undergone enantioselective annulation reaction to afford respective tetrahydropyridines **3f-3j** in relatively lower 50-63% yields with 72-97% *ee* 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* ratio upto 1:2. Alkyl substituted allenes **2e, 2i** offered alkyl-substituted tetrahydropyridines **3e, 3i** in nearly same yields, however, with relatively lower *ee* (78 and 72%).

It seems the trifluorosulfonyl (-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 secondary 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 3). To our delight, ferrocenyl secondary amines **1b-1e** having methyl, ortho-nitrophenyl, 3,5-diflorophenyl, para-methyl-phenyl sulfonyl also underwent enantioselective C-H-annulation leading diversely *N*-substituted chiral

Scheme 4. Substrate Scope of Amines Derivatization



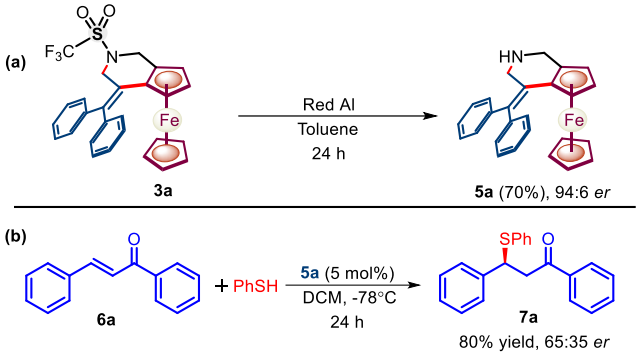
Reaction conditions: (a) **1a** (0.14 mmol), **2a** (0.28 mmol), $Pd(OAc)_2$ (0.0112 mmol), NOBINAc (0.039 mmol), CsF (0.28 mmol), CuO (0.14 mmol) THF (1 mL), dry air, 75°C, 18 h. (b) Isolated yield of the product was determined by column purification. (c) The *ee* of the product was determined by HPLC analysis. (d) E:Z was determined by ^{1}H NMR Analysis

tetrahydropyridines **3k**-**3z** ranging yields of 28-58% with 72-98% *ee*. Whereas nosyl and SO_2CH_3 protected amines yielded ferrocene fused tetrahydropyridines **3t**-**3y** relatively lower yields 28-42% with 72-94% *ee* (Scheme 4). However, acetyl protected ferrocenyl secondary amine **1f** failed to afford any annulated ferrocene.

Further, 1-phenyl-1-propyne and ethyl acrylate coupling partners, which could react through π-interaction with in-situ formed

proposed metallacycle, were explored under the NOBINAc-accelerated reaction conditions. Gratifyingly, ethyl acrylate underwent an enantioselective C-H activation reaction to provide dehydrogenative Heck-coupled ferrocenyl acrylate **4a** in 35% yield and 82% *ee* under the optimized reaction conditions. On the other hand, 1-phenyl-1-propyne provides traces of annulated product under the optimized conditions.

Scheme 5. Post Derivatization and Application of Ferrocene fused Chiral Amine as a Catalyst

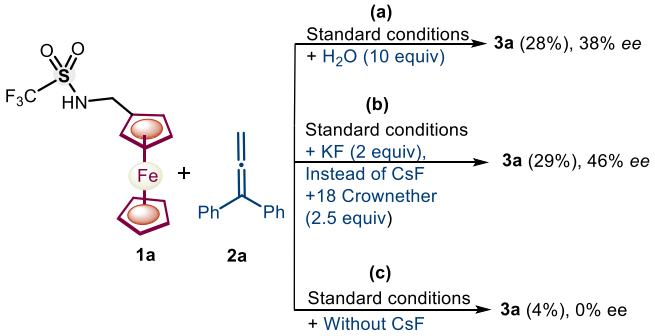


Reaction condition: (**a**) **3a** (0.05 mmol), Red Al (0.5 mmol), in dry Toluene, 50ºC, 20 h. (**b**) **6a** (0.1 mmol), PhSH (0.25 mmol), **5a** (0.005 mmol), in dry DCM, -78ºC, 24 h.

Next, we have shown that the sulfonyl protection at the amine backbone can be readily eliminated from synthesized chiral **3b**, affording unprotected tetrahydropyridine **5a** with a 70% yield and 94:6 *er*. The utility of the synthesized chiral ferrocene fused amine has been shown as a catalyst for enantioselective thia-Michael reaction with chalcone **6a** providing **7a** upto 80% yield and 65:35 *er*.

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 6). 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 6). On the other hand, complete negligence in the reaction was observed in the absence of cation (condition c, Scheme 6). 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).

Scheme 6. Control Experiments for Secondary Cationic Interaction on NOBINAc Catalysis



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 72).

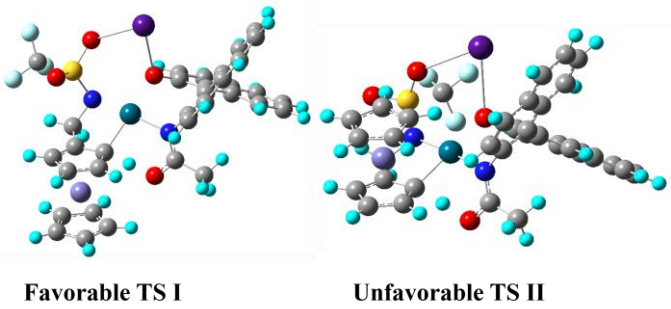
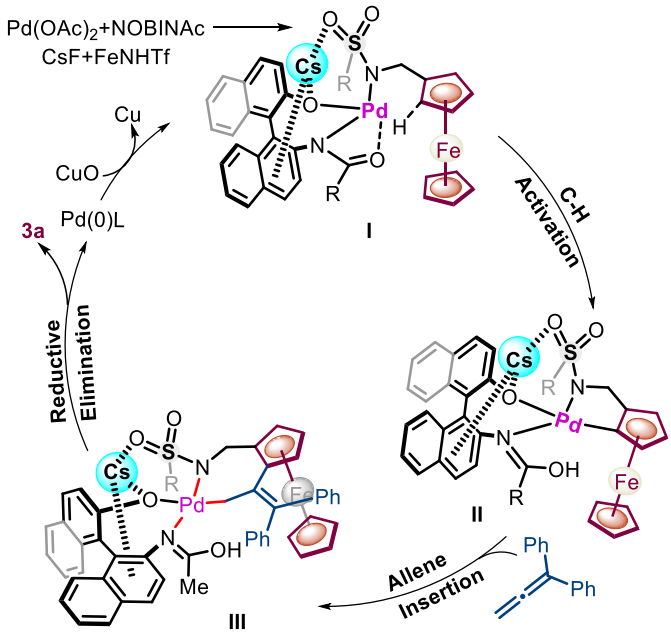


Figure 2. DFT Computation for (I) Favorable and (II) Unfavorable Transition State. [a] The optimization of the proposed structures derived from **1a**, Pd(II), *S*-NOBINAc and Cs^+ and the energies were obtained at a DFT-B3LYP/6-311+g(d,p)/LANL2DZ level of theory.

Next, the DFT computations were carried out to shed light on the steric effect for high enantioselective discrimination. 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 crowding. The relative energy difference of **2.84 kcal/mol** was realized between favorable **TS1** and unfavorable **TS2** (Figure 2).

Scheme 7. Catalytic Cycle for C-H Annulation



In the proposed catalytic cycle (Scheme 7), the initial step seems to involve secondary cationic interaction between sulfonate and ligand **L10**, enabling the generation of a chiral catalytic pocket in palladium intermediate **I**.

Enantiodetermining C-H activation step *via* the concerted metalation deprotonation (CMD) process led to palladacycle **II**. Subsequently, palladacycle **II** might undergo allene insertion

followed by migratory insertion to form palladacycle **III**. Ultimately, reductive elimination could afford annulated ferrocene **3a** with concomitant release of the catalyst.

In summary, we have revealed secondary cationic interactions driven by an efficient NOBINAc ligand and ferrocenyl secondary amines affinity for a highly enantioselective C-H activation and annulation process. Furthermore, secondary amines having sulfonyl group seem crucial for high enantioselective induction; consequently, a variety of sulfonyl groups (-SO_2-R) has been exploited for C-H activation. The subsequent annulation enables the development of an efficient methodology for synthesizing chiral ferrocene-fused tetrahydropyridine derivatives with the variation of allenes. The sulfonyl protecting group can be effortlessly removed to provide chiral ferrocenyl secondary amine, which shows the potential application as a chiral catalyst. Initial results allowed us to explore the π-mode of activation within allenes and acrylate. 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, characterization data, and copies of ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR of all the synthesized compounds (PDF)

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

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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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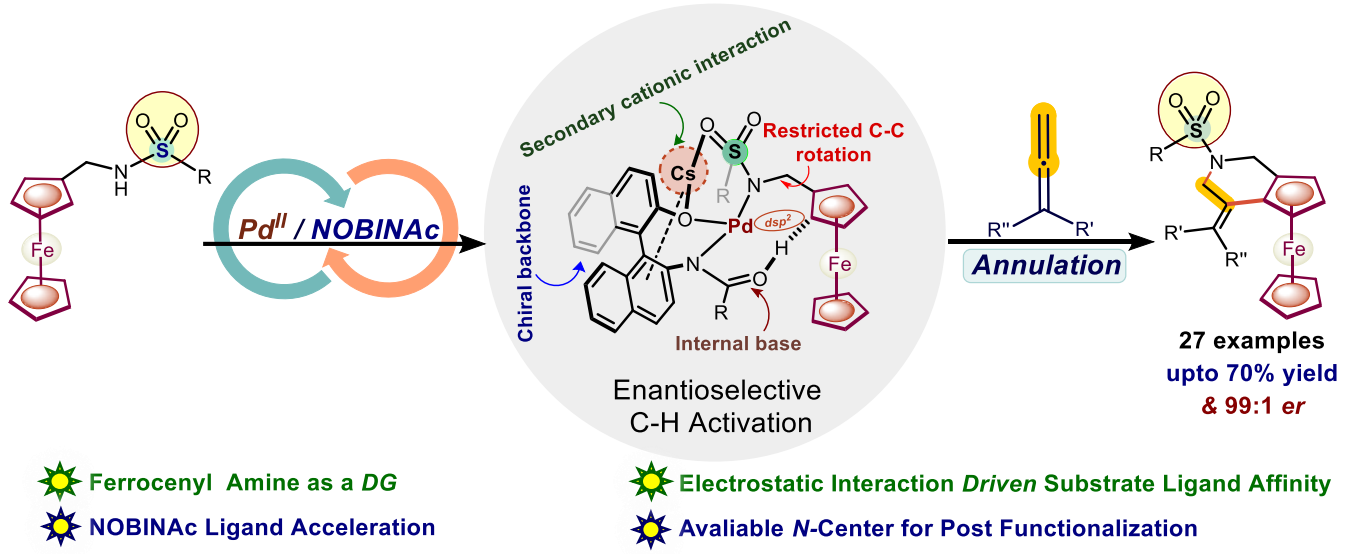

- Ferrocenyl Amine as a *DG*
- NOBINAc Ligand Acceleration
- Electrostatic Interaction *Driven* Substrate Ligand Affinity
- Avaliable *N*-Center for Post Functionalization