Rh(III)-Catalyzed [4+3] Annulation: Temperature Dependent Stereodivergent Synthesis of Point-Planar Chiral Ferrocene Fused Azepines

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KEYWORDS: [4+3] Annulation, Allenes, Enantioselectivity, Stereodivergent, Planar Chiral Ferrocene.

ABSTRACT: Planar chiral ferrocenes are extensively investigated structures in asymmetric catalysis, materials science, and medicinal chemistry. Although the synthetic approaches for six-membered fused planar chiral ferrocenes are well-established, the construction of a seven-membered fused ring *via* [4+3] annulation has remained unexplored and seems to be challenging. Herein, an efficient rhodium-catalyzed temperature-dependent stereodivergent [4+3] annulation reaction has been developed for the synthesis of novel seven-membered ferrocenylazepines *via* C-H activation of substituted ferrocene-*p*-tosylamides with allenes. At room temperature, Rh-catalyzed [4+3] annulation selectively offered one diastereomer (>20:1 dr), whereas at 60 ºC, another diastereomer was obtained exclusively (>20:1 dr). Further, [4+3] annulation reaction in the presence of chiral $RhCp^X$ catalyst (2 mol %) yielded chiral ferrocenyl azepines in 56% yield and up to 90:10 er. Mechanistic investigations by control experiments, isotopic labelling study, and DFT computation suggested that the reaction proceeds *via* a formation of a σ-bonded rhodacycle, having low energy due to less steric repulsion between the phenyl ring of allene and Cp*(pentamethyl cyclopentadienyl), which upon reductive elimination offered kinetically controlled diastereomer. Under heating (60 ºC) conditions and in the presence of a base, kinetically controlled diastereomer could undergo CH-allylic isomerization to afford completely thermodynamic controlled diastereomer, which has also been observed experimentally.

Introduction

Ferrocene, an organometallic sandwich complex, shows excellent chemical stability and redox properties.[1,2] It possesses quintessential planar chirality,[3] consequently, planar chiral ferrocenes (PCFs) are among the most explored examples of planar chirality and serve as an excellent ligands in asymmetric catalysis (Figure 1).[4-8] Among them, the Josiphos ligand is being used in industry for asymmetric hydrogenation of alkenes.[9] The continued advancement of ferrocene-fused nitrogen heterocycles represents a significant class of molecules utilized as catalysts in asymmetric transformations.[10] These include ferrocene-fused DMAP,[5] bipyridine, and pyridine *N*-oxide, enabling kinetic resolution of secondary alcohols, chiral cyclopropane synthesis, and ring-opening reactions.[11] Additionally, ferrocene-fused imidazolium salts[7] serve as chiral NHC ligands in alkene borylation, leading to a very high level of enantioselectivity. Despite the high demand of heterocyclic fused ferrocenes (Figure 1), the synthesis of these fused systems is difficult and requires intricate multistep synthetic protocols.

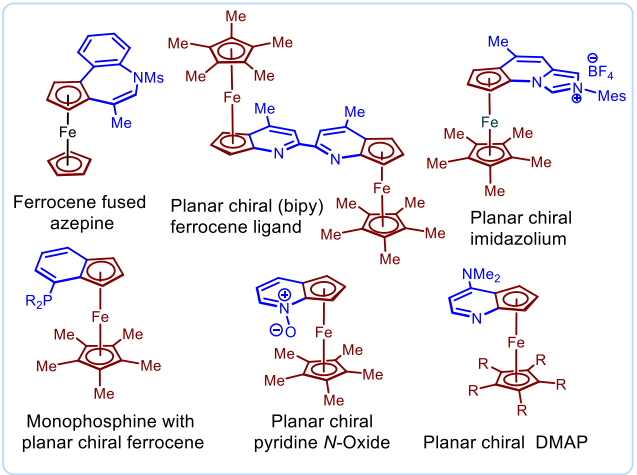
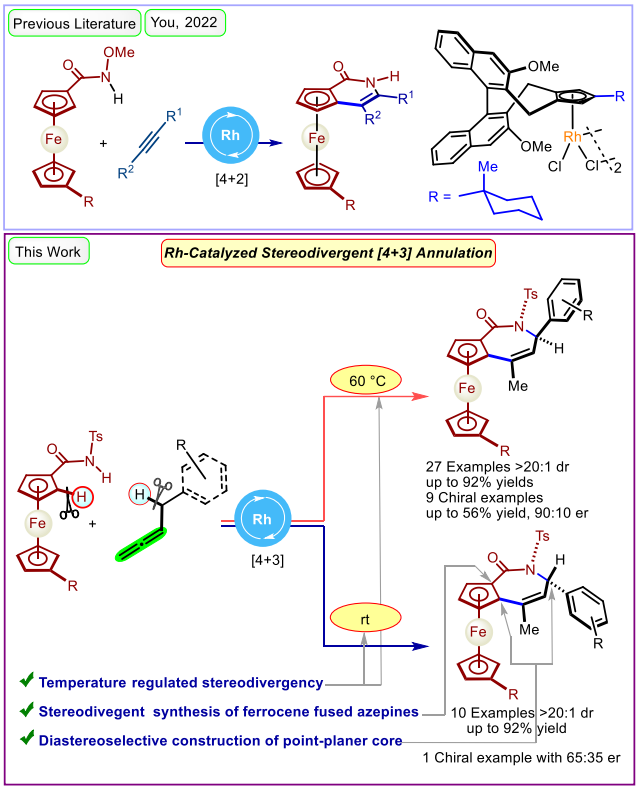


Figure 1. Depiction of Chiral Ferrocene Fused Heterocycles in Asymmetric synthesis.



Scheme 1. Synthesis of Chiral Fused Ferrocene.

Over the past few decades, many advances have been made in the field of transition metal-catalyzed asymmetric C-H functionalization to synthesize chiral ferrocene[3, 12-15] over the conventional methods, namely enantioselective *ortho*-lithiation[16-21] and chiral resolutions.[22-23] Consequently, a variety of directing groups and coupling partners have been explored under chiral Rh,[24-27] Pd,[28-32] Ir,[33,34] Pt,[35] and Sc-based catalysis.[36] Initially, intramolecular annulation methodology was employed for the synthesis of planar chiral five or six-membered ferrocene-fused rings. Shibata[35] *et al.* have synthesized enantioselective intramolecular planar chiral ferrocene fused azepines employing Pt-catalyzed cycloisomerization. Heterocyclic azepine core is present in various natural products, namely carbamazepine and darenzepine, mirtazapine, and oxcarbazepine seven-membered heterocycles are being used as drugs and agrochemicals.[37-38]

The necessity of a designed pre-installed directing group limits the versatility of such approaches; however, tethered substrates enabled the effective synthesis of ferrocene-fused heterocycles by C-H activation.[35,39-42] Direct C-H activation and subsequent annulation provide a route for the intermolecular version of such annulation, where another coupling partner can be introduced to access highly substituted complex chiral fused compounds in an efficient way. Very recently, You and co-workers[43] constructed chiral fused ferrocenes by using alkyne as a coupling partner in an [4+2] annulation reaction employing Cramer chiral Rh-catalysts (Scheme 1). Next, the choice of coupling partner in direct C-H activation/annulation reactions significantly influences the unique structural modifications in fused planar chiral ferrocenes. For example, allene exhibits the potential to modulate such annulation reactions having three carbon synthons leading to distinct chemo-, regio-, and diastereoselective pathways based on the specific reaction conditions and employed catalysts.[31, 44-46] These modulation are already well-known in a variety of other aromatic systems, particularly [4+1][18], [4+2][19], and [3+3][47] type annulation. However, it is crucial to address the challenges related to regiocontrol and the inherent instability of allene during the reaction. Despite these challenges, it provides the opportunity to introduce one more chiral center associated with the planar chirality in ferrocenes.

Controlling absolute and relative configurations in a reaction that afford multiple stereogenic centers remains elusive, as the synthesis of one of the diastereomer may be possible, but the other corresponding complementary diastereomer is difficult; consequently, the reaction becomes non-stereodivergent.[48-50] The stereodivergence pathways can yield multiple products having multiple stereocenters from the same starting material, whereas in diastereodivergence selective formation of two or more diastereomers is possible. The synthetic potential of diastereo and stereodivergence has been revealed in many fundamental reactions and synthetic strategies.[51-53]

Our group has studied the C-H activation in ferrocene for the construction of C-C and C-S/Se/Te bonds.[54-60] However, enantioselective C-H functionalization has not been achieved by us. Further, a variety of directing groups have been studied along with various coupling partners, namely alkanes, arenes, aryl halides, alkenes, and alkynes, by others and us.[43,54-60] However, allenes have not been explored to date. Herein, we report for the first time an Rh-catalyzed temperature dependant stereodivegence synthesis of ferrocene fused azepines *via* allene driven [4+3] annulation. This protocol offers to synthesize kinetically and thermodynamically controlled diastereomers at room and high temperatures, respectively. Further, seven-membered azepine heterocycles have been constructed enantioselectively by using a chiral $RhCp^X$-catalyst for the first time. Control experiments and DFT computations have also been performed to gain insight into the temperature-dependent diastereodivergent construction of seven-membered fused azepines.

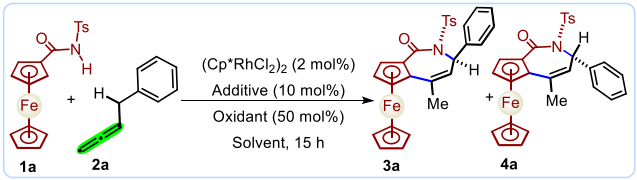
Results and Discussion

Reaction development

N-Tosylcarboxamide directing group (DG) was selected over earlier used bidentate *N*-8-aminoquinolinyl[58] and *N*-aryl/alkyl carboxamides DGs[58] to obtain the desirable selectivity and reactivity, respectively. A well-known bidentate *N*-8-aminoquinolinyl directing ligand facilitates C-H activation effectively and exhibits very good reactivity,[61-63] however, it offers poor selectivity, presumably due to the ligand rigidity. Consequently, *N*-tosylferrocenecarboxamide substrate **1a** was prepared from ferrocenoyl chloride and *p*-tosylsulfonamide in ethyl acetate solvent (See SI 6).[64] We started our investigation for Rh-catalyzed annulation with *N*-tosyl ferrocenecarboxamide **1a** and benzylallene **2a** as a model substrate in the presence of a mild oxidant AgOAc (Table 1). The reaction was carried out in non-polar solvent toluene at 80 °C which resulted in a [4+3] fused azepine **3a** in 5% yield with excellent diastereoselectivity (dr) >20:1 (entry 1, Table 1). The addition of the strong oxidant $Cu(OAc)_2$ along with AgOAc oxidant to the reaction resulted in an improvement of 5% yield of **3a** (entry 1 *vs* 2, Table 1), which suggested that the catalyst may not be taking part in the reaction as regeneration may not be a concern in the presence of AgOAc oxidant. The formation of the cationic active rhodium catalyst may be required. Consequently, a strong halide scavenger $AgBF_4$ was introduced to the reaction, leading to a further yield

enhancement to 22% (entry 3, Table 1). The unsatisfactory performance of toluene as a solvent in the reaction leads us to conduct a systematic solvent screening.

Table 1. Optimization of the Reaction Conditions for Rhodium-Catalyzed [4+3] Annulation[a]



Entry	Additive	Solvent	Temp.	Yield[c] **3a**	Yield[c] **4a**
1	-	toluene	80	5	-
2	AgOAc	toluene	80	15	-
3	$AgBF_4$	toluene	80	22	-
4	$AgBF_4$	DCE	80	NR	-
5	$AgBF_4$	^{t}BuCN	80	35	-
6	$AgBF_4$	MeCN	80	46	-
7	$AgPF_6$	MeCN	80	35	-
8	$AgSbF_6$	MeCN	80	40	-
9	$AgBF_4$	MeCN	60	65	-
10[b]	**$AgBF_4$**	**MeCN**	**60**	**92**	**-**
11[c]	$AgBF_4$	MeCN	40	72	16
12[c]	**$AgBF_4$**	**MeCN**	**RT**	**-**	**88**

[a] Reaction conditions: **1a** (0.13 mmol), **2a** (2 equiv.), $(Cp^*RhCl_2)_2$ (0.002 mmol), additive (10 mol %), oxidant (50 mol %), 2 mL solvent at 60 °C. [b] NaOPiv (1 equiv).[c] Isolated yield

The coordinating polar aprotic nitrile solvents were found to be more effective than the others, affording 46% yield, possibly due to their ability to stabilize the reactive intermediates involved in the [4+3] annulation (entries 4-6, Table 1). Further, $AgSbF_6$ and $AgPF_6$ halide scavengers were also evaluated in the reaction, which led to lower 35 and 40% yields of **3a**, respectively (entries 7-8, Table 1).

Previous literature[65] on allene transformations suggested that the reactivity of allenes could be a concern, as it readily undergoes degradation and polymerization at higher temperatures. Therefore, to mitigate these side reactions, lowering the temperature from 80 to 60 °C led to a moderate enhancement in the yield (65%) of **3a** (entry 9, Table 1). To our delight, an addition of NaOPiv salt (1 equiv) resulted in a very good yield (92%) with excellent *dr* (>20:1) of **3a** (entry 10, Table 1). Here, NaOPiv seems to act as an internal base in this reaction which increases the rate of the concerted metalation deprotonation (CMD) step.[66] Additionally, it shifts the equilibrium towards the metallacycle formation (*vide infra*). Surprisingly, a decrease in the diastereomeric ratio (4.5:1) was realized when the reaction was conducted at 40 °C during the temperature optimization (entry 11, Table 1). This result suggested that the formation of another diastereomer **4a** is also feasible. Next, the reaction at room temperature resulted in another diastereomer **4a** in 88% yield with an excellent dr (>20:1, entry 12, Table 1) to our delight. Both of the diastereomers **3a** and **4a** were studied by single crystal X-ray diffraction analysis (Figure 2).

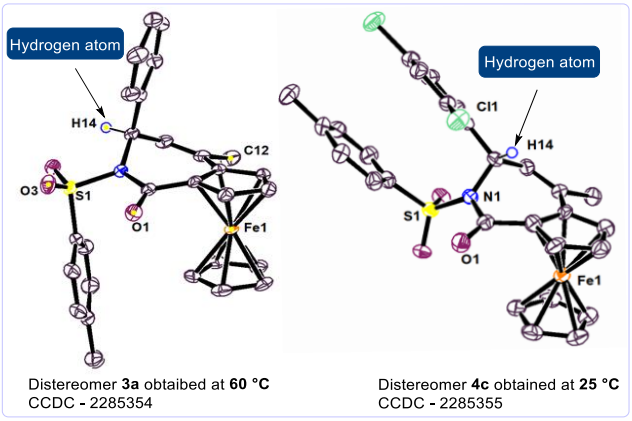
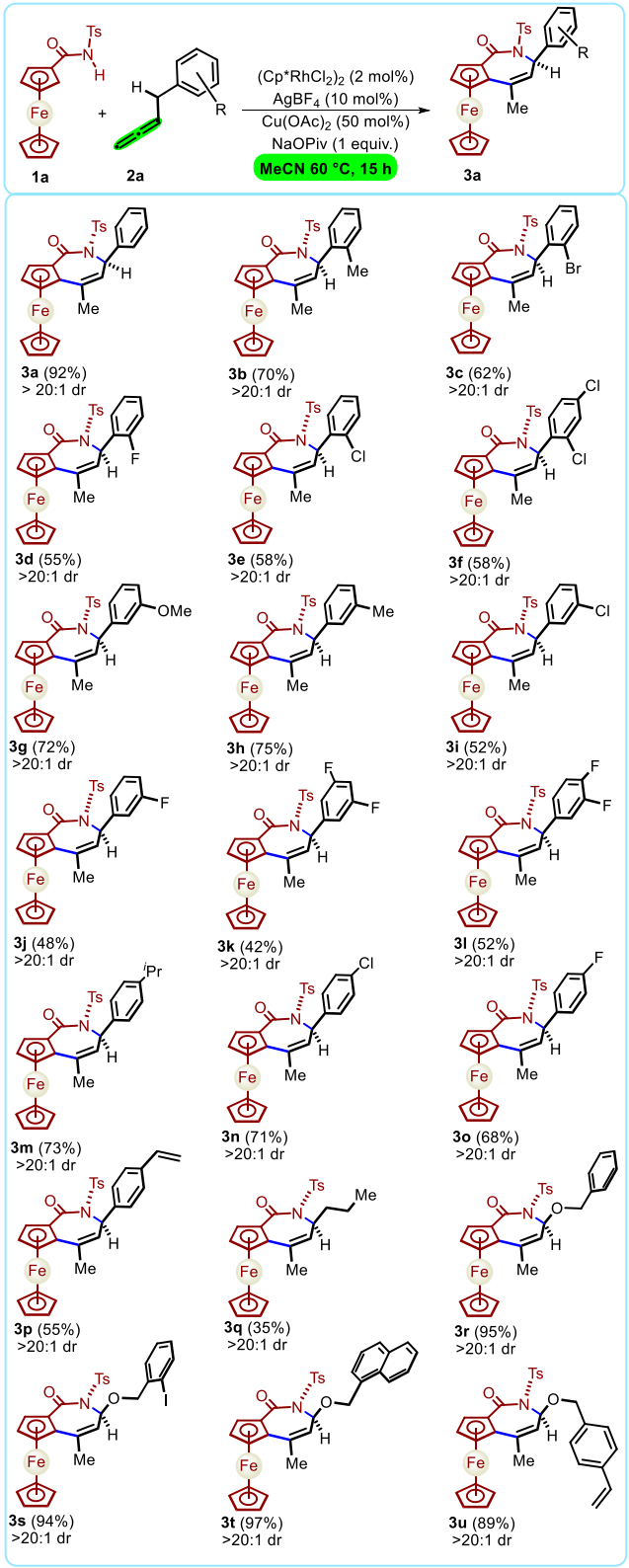


Figure 2. ORTEP Views of **3a** and **4c** with 50% Ellipsoid Probability. The phenyl ring (came from allene) in **3a** is situated above side and hydrogen is down side. In the diastereomer **4c** which is obtained at 25 °C, phenyl ring of allene is downside and hydrogen is up side. Rest of the hydrogen atoms are omitted for clarity.

After optimizing the conditions for both diastereomers **3a** and **4a**, we investigated the scope of the reaction with regard to different allenes at 60 °C. Initially, in benzyl allenes, *ortho*-methyl substitution provided a good yield of **3b** (70%) with an excellent dr >20:1. While allenes with electron-withdrawing bromo, fluoro, and chloro-substitution in phenyl ring provided [4+3] annulated ferrocene fused azepines (**3c**-**3f**) in moderate 55-62% yields with an excellent diastereomeric ratio >20:1. Further, *meta*-substitution in phenyl ring with electron-donating groups (EDGs) provided moderate to good yields of **3g** (72%) and **3h** (75%). Conversely, electron-withdrawing groups (EWGs) at *meta* position in phenyl allenes provided moderate yields (52-65%) of **3i-3l** with excellent dr (>20:1).

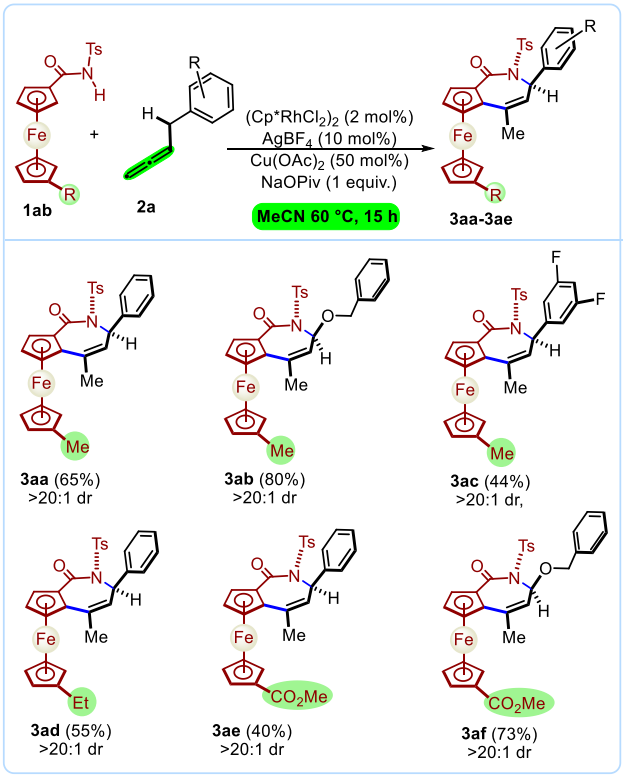
Moreover, the *para*-substituted allene with electron-donating ^{i}Pr and withdrawing fluoro and chloro substituents offered better yields (68-73%) of [4+3] annulated ferrocene fused azepines **3m-3o**. We also explored styrene-based allene substrate having alkene moiety under Rh-catalyzed [4+3] diastereoselective annulation reaction. To our delight, the reaction afforded desired [4+3] ferrocene fused azepines 3p chemoselectively, albeit a slight reduction in the yield (55%) was observed. The insight from the substitution in the phenyl ring of allene studies indicated that both electronic and steric factors seem important in Rh-catalyzed [4+3] annulation. However, steric factors appear to be dominant than electronic factors. Next, aliphatic allene, a challenging substrate in Cp*M-catalyzed annulation,[67] was subjected to [4+3] annulation reaction, which provided a poor yield (35%) of alkyl azepine **3q** (Scheme 2). Further, *iso*pentyl allene reacted sluggishly in the reaction, and respective [4+3] annulated azepine could not be isolated, presumably due to the steric of *iso*propyl substituent. Desirably, heteroatom (benzyloxy, *ortho*-iodophenyl, naphthalene, and *para*-styrene) substituted allenes provided respective



Scheme 2. Substrate scope for [4+3] Annulation [a] Reaction conditions: **1a** (0.13 mmol), **2a** (2 equiv.), $(Cp^*RhCl_2)_2$ (2 mol%), $AgBF_4$ (10 mol%), $Cu(OAc)_2$ (50 mol%), NaOPiv (1 equiv), 2 mL solvent at 60°C.

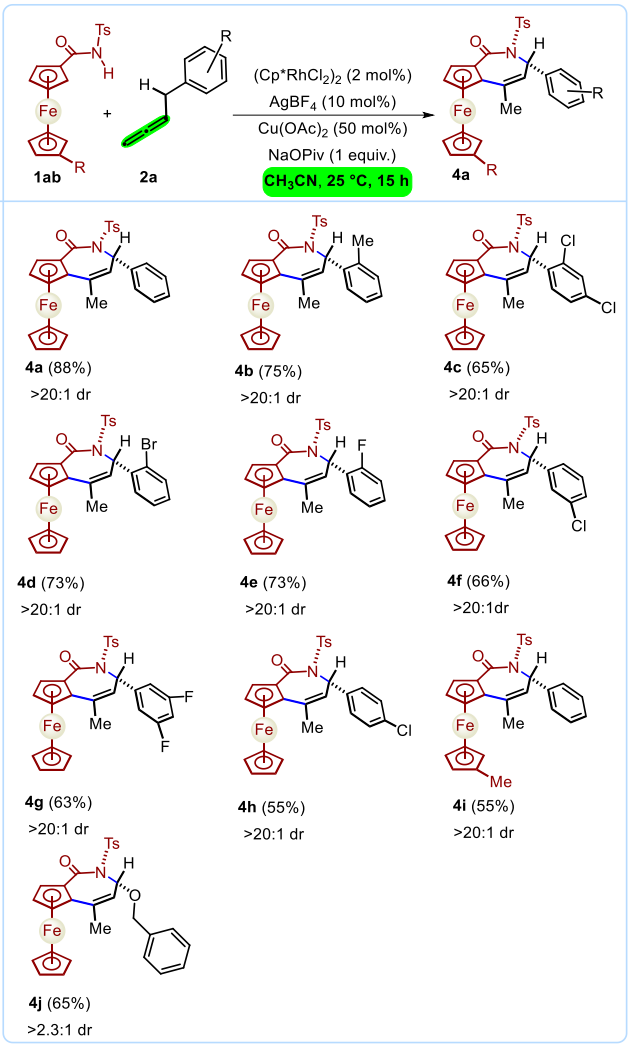
ferrocene fused azepines **3r-3u** in excellent yields (89-97%) and excellent >20:1 dr. However, steric factors appear to be dominant than electronic factors. Next, aliphatic allene, a challenging substrate in Cp*M-catalyzed annulation,[67] was subjected to [4+3] annulation reaction which provided a poor yield (35%) of alkyl azepine **3q** (Scheme 2). Further, *iso*pentyl allene reacted sluggishly in the reaction and respective [4+3] annulated azepine could not be isolated presumably due to the steric of *iso*propyl substituent. Desirably, heteroatom (benzyloxy, *ortho*-iodophenyl, naphthalene, and *para*-styrene) substituted allenes provided respective ferrocene fused azepines **3r-3u** in excellent yields (89-97%) and excellent >20:1 dr. A substantial increase in the yield using oxygen-heteroatom substituted allenes (Bn-O-$C\underline{H_2}$-CH=C=CH_2) suggested that the high acidity of sp^3-C-H bond in allenes could facilitate [4+3] annulation.

Subsequently, the reactions of substituted *N*-tosylferrocencarboxamide having methyl and carboxymethyl on the second Cp ring were explored under the Rh-catalyzed reaction conditions (Scheme 3). Here, observed that increasing the steric crowd on the second Cp ring slower the reactivity. Though, alkyl-substituted *N*-tosylferrocencarboxamide with various allenes provided good yields ranging from 44 to 80% of substituted ferrocene [4+3] annulated azepines **3aa-3ad**, and the carboxymethyl substituted ferrocene substrate afforded a moderate yield (40 and 73%) of annulated azepines products **3ae** and **3af** with unaltered diastereoselectivity(>20:1).



Scheme 3 Substrate scope for [4+3] Annulation with regards to Substitution in Ferrocene [a] Reaction conditions: **1ab** (0.13 mmol), **2a** (2 equiv.), $(Cp^*RhCl_2)_2$ (2 mol%), $AgBF_4$ (10 mol%), $Cu(OAc)_2$ (50 mol%), NaOPiv (1 equiv), 2 mL solvent at 60°C.

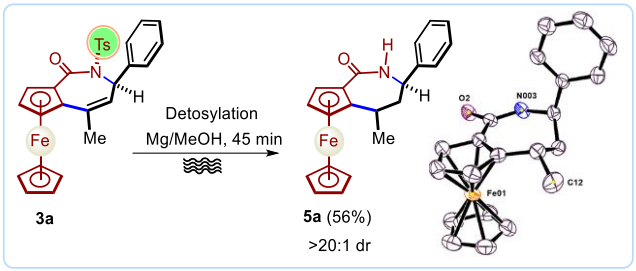
Next, the substrate scope has been explored to isolate another diastereomer at room temperature (Table 1, entry 10). Initially, phenyl allene afforded a good yield (65%) of **4a** with an excellent diastereomeric ratio (>20:1) (Scheme 4).



Scheme 4. Substrate scope for [4+3] Annulation [a] Reaction conditions: **1a** (0.13 mmol), **2a** (2 equiv.), $(Cp^*RhCl_2)_2$ (2 mol%), $AgBF_4$ (10 mol%), $Cu(OAc)_2$ (50 mol%), NaOPiv (1 equiv), 2 mL solvent at 23°C

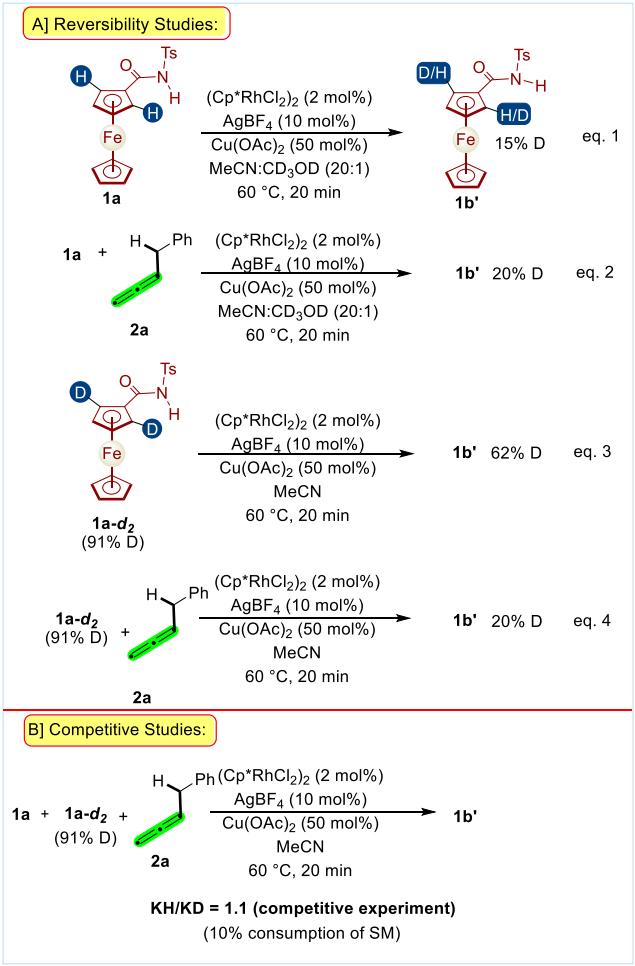
Subsequently, the introduction of an electron-donating *ortho*-methyl substituent resulted in a 75% yield of annulated azepine **4b**. Conversely, the electron-withdrawing substituents like chloro, bromo, and fluoro, led to slightly reduced yields ranging from 65-66% of **4c-4e**, with an excellent diastereomeric ratio. *Meta*-substituted electron-withdrawing groups also proved effective, yielding ferrocene fused azepines **4f** and **4g** in 63% and 55%, respectively. Hetero-substituted allenes afforded an excellent yield, albeit with a slightly reduced diastereomeric ratio due to the allylic acidic C-H (Scheme 4).

Further, the product derivatization of seven-membered ferrocene azepine was modified by the removal of the *N*-tosyl group for manipulating a variety of late-stage transformations. In our first attempt, the removal of the *N*-tosyl group by the well-established samarium iodide method failed. Instead of cleaving *N*-tosyl group, a complex mixture was observed. Alternatively, Mg in CH_3OH has been used under the sonication condition; the seven-membered ferrocene azepine **3a** underwent tosyl cleavage followed by alkene reduction in one part, finally afforded N-H containing a novel tetrahydro ferrocene fused azepines **5a** in 56% yield with intact diastereoselectivity (>20:1) (Scheme 5). The newly obtained tetrahydro ferrocene fused benzo azepines **5a** was characterized by single crystal X-ray diffraction analysis.



Scheme 5. ORTEP View of **5a** with 50% ellipsoid probability, hydrogen atoms omitted for clarity. CCDC deposition number = 2285356. Hydrogen atoms were omitted for clarity.

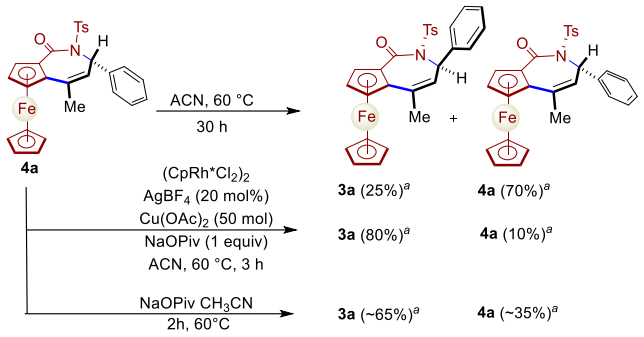
To gain mechanistic insight into the selective formation of the unexpected fused seven-membered heterocyclic ring over a five-membered and to understand the temperature-dependent diastereoselectivity, various control experiments were carried out (Scheme 6). To check the reversibility of C-H metalation, the reaction was performed with deuterated methanol-d_4, which afforded deuteration at both *ortho* positions of *N*-tosyl ferrocenecarboxamide **1a** (eq 1, Scheme 6). Similarly, the C-H metalation of *N*-tosyl ferroceneamide in the presence of CD_3OD and allene coupling partner showed reversible deuteration (eq 2, Scheme 6).



Scheme 6. Control experiments and Studies to Check for a Kinetic Isotope effect.

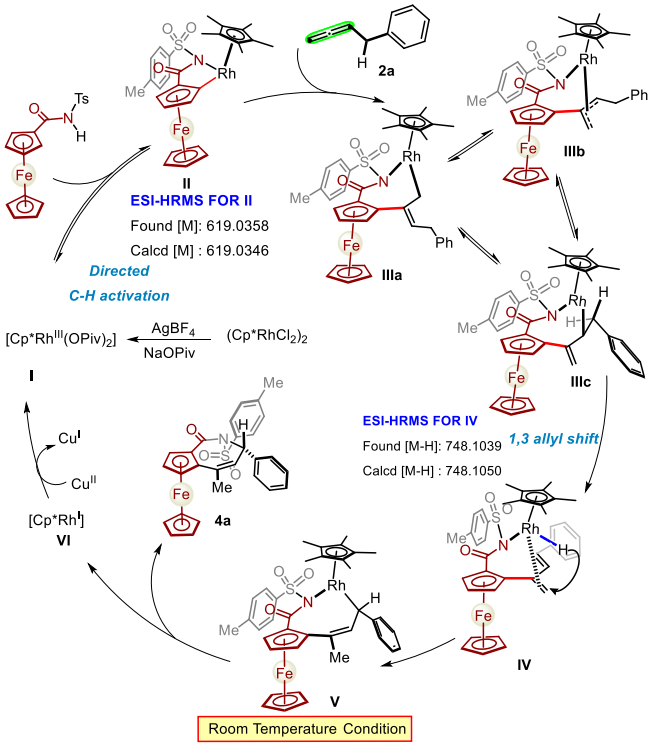
https://doi.org/10.26434/chemrxiv-2023-918dp **ORCID:** https://orcid.org/0000-0003-0658-8709

Further, labeled *ortho* deuterated (91% deuteration) tosyl-ferrocene carboxamide **1a-*d*$_2$** was prepared and subjected to deuterium-hydrogen exchange in acetonitrile. This reaction also provided the loss of deuterium from **1a-*d*$_2$**, suggesting that the C-H activation was a reversible process (eq 3, Scheme 6). Similarly, C-H metalation of *N*-tosyl ferroceneamide **1a-*d*$_2$** in the presence of an allene coupling partner showed the reversible deuteration in acetonitrile (eq 4, Scheme 6). To investigate whether the C-H metalation step was a rate-determining step, kinetic isotopic studies were carried out. A k_H/k_D value of 1.1 suggested that the concerted metalation deprotonation (CMD) might be the rate-determining step.



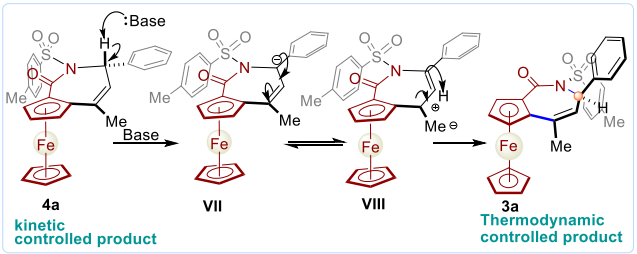
Scheme 7. Control Experiments for the Conversion of Kinetically Controlled Diatsereomer **4a** into **3a**. [a] NMR yield

To gain more insights on temperature dependent selective diastereomer construction of ferrocenyl azepines, the control experiments have been carried out on isolated diastereomer **4a**, which is obtained at room temperature (Scheme 7). Kinetically controlled diastereomer **4a** upon heating alone in acetonitrile for 30 h afforded only 25% yield of thermodynamically controlled diastereomer **3a**. Whereas in the presence of $(CpRh^*Cl_2)_2$ catalyst, diastereomer **4a** has converted in thermodynamic controlled diastereomer **3a** efficiently and afforded 80% yield in 3 h. Based on the control experiments, isotopic labelling studies, and DFT computation (*vide infra*), a tentative mechanism is then proposed for Rh-catalyzed diastereodivergent synthesis of ferrocene-fused azepines from *N*-tosylferrocene carboxamide and allenes (Scheme 8). Initially, $[Cp^*Rh^{III}Cl_2]$ dimer undergoes ligand exchange with sodium pivalate (NaOPiv) in the presence of $AgBF_4$, to form an active $Cp^*Rh^{III}(OPiv)_2$ **I** catalyst. Subsequently, acidic NH bond of the substrate **1a** would exchange with the OPiv ligand of $Cp^*Rh^{III}(OPiv)_2$ **I** to afford Rh-amidate type of intermediate, subsequently, activation of C-H bond *via* concerted metalation deprotonation (CMD) could generate rhodacycle **II**. Further, interaction of rhodacycle **II** with the allene and subsequent migratory insertion of allene into the Rh-C bond could generate σ-rhodium allylic species **IIIa**. This would transform into π-rhodium η^3-allylic species **IIIb** which may further isomerize to σ-rhodium allylic species **IIIc** having Rh-C σ-bond adjacent to the benzylic position.[68] The *in-situ* formation of rhodacycle **II** (observed mass = 619.0358) and intermediate **III** (observed mass = 748.1039)[69] was also studied by mass spectrometry. Further, *β*-H elimination led to the formation of rhodium hydride followed by a 1,3 allyl shift could afford η^2 π -alkene-Rh-hydride intermediate **IV**.[70] Intramolecular hydride transfer to the terminal carbon of alkene could lead to a π-allyl-type Rh **V** in an unprecedented manner. Next, π-allyl-type Rh intermediate **V** converted into 8-membered σ-bonded rhodacycle **VI,** which, upon reductive elimination, afforded the desired kinetically controlled seven-membered ferrocene fused azepine **4a** with concomitant release of Rh(I). Rh(I) could be oxidized by Cu(II) acetate to regenerate Rh(III) catalyst.



Scheme 8. Proposed Mechanism for Rh-Catalyzed [4+3] Temperature-Controlled Annulation of Ferrocene. The mass values for intermediates **III** to **VI** are the same. The reaction mixture was subjected for mass analysis after 15 minutes of mixing of allene with ferroceneamide **1a** under Rh-catalyzed conditions.

Alternatively, the kinetic-controlled diastereomer could isomerize into the thermodynamic-controlled product via base-mediated thermal isomerization (Scheme 9). Initially, a proton is abstracted from **4a** by the base, leading to the formation of allylic anion species **VII**, which interconvert into **VIII** by resonance. The allylic anion **VIII** would accept a proton from the below side to lead the formation of the thermodynamic-controlled diastereomer **3a**.

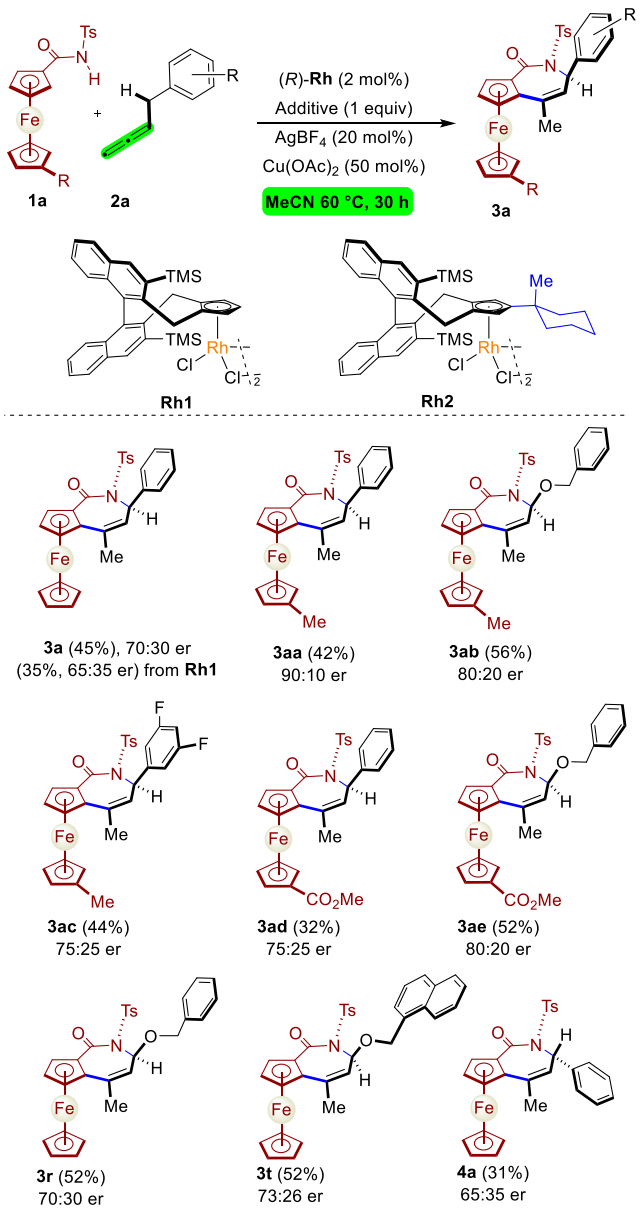


Scheme 9. Base Mediated Thermal Isomerization of Kinetically Controlled **4a** into Thermodynamically Controlled **3a**.

Worth noticing that the except the seven-membered ring-sized ferrocene fused azepenes, the formation of five or six-membered isoindolinone or dihydroisoquinoline ring was not observed under the Rh-catalyzed reaction conditions and could

be attributed to the angle ring strain generated it from Cp-ring of ferrocene.

Next, we explore the stereodiveregent synthesis of seven-membered ferrocene fused azepines. Worth noticing that the enantioselective ring construction of seven-membered ring heterocycles, in general, and azepines, in particular, has not been studied despite myriad enantioselective studies of five and six-membered ring construction.[17-19]



Scheme 10 Enantioselective [4+3] Annulation for the Construction of Chiral Ferrocene Fused Azepines. For isolating product **4a**, reaction condition was carried out at room temperature.

To achieve the asymmetric version of the azepine core, our group has drawn inspiration from the extensive designing of chiral C_2 symmetric cyclopentadienyl-rhodium-based Cramer's catalysts. Cramer *et al*. have prepared chiral Co,[71] Rh,[68, 70, 72] and Ir[73-74]-catalysts with Cp^X ligands and have been applied in various asymmetric synthetic methodologies. We have prepared the trimethyl silyl substituted back wall containing cyclopentadienyl chiral Cramer catalyst **Rh1**.[75] A cyclohexyl substituted front wall and trimethyl silyl substituted back wall consisting of cyclopentadienyl chiral $RhCp^X$ catalyst **Rh2** has also been prepared for [4+3] annulation reaction (Scheme 10).

We initially subjected **Rh1** catalyst to the optimized reaction conditions, which resulted in the formation of seven-membered ferrocene azepine **3a** with a yield of 35% and an enantioselectivity of 60:40 er (Scheme 10). Using catalyst **Rh2** under the same optimized reaction conditions, a slight improvement in the yield (45%) of **3a** along with enhanced enantioselectivity of 70:30 er were realized (see ESI, page S10). Based on a literature survey,[43] we envisioned that the substitution on the other cyclopentadienyl ring of ferrocene may offer an alternative strategy to enhance enantioselectivity. Consequently, we prepared methyl and carboxymethyl-substituted *N*-tosyl ferroceneamides (**1b-1d**) and subjected them to **Rh2**-catalyzed optimized reaction conditions (Scheme 10). A marked improvement in the enantioselectivity was observed with **1b-1d** substrates leading to **3aa** and **3ad** with an enantiomeric ratio of 90:10 and 75:25, respectively (Scheme 10). Next, we attempted the reaction at room temperature catalyzed by chiral **Rh2**-catalyst to obtain an enantioenriched kinetically controlled diastereomer. The reaction of ferrocenecarboxamide **1a** with allene under **Rh2**-catalyzed [4+3] annulation afforded chiral kinetically controlled diastereomer **4a** with 65:35 er and 31% yield (Scheme 10).

Conclusion

In conclusion, we have established a RhCp* catalyzed temperature-controlled stereodivergent regioselective intermolecular [4+3] annulation of *N*-tosylferrocene carboxamide with allenes. The developed C-H and C-N annulation reaction proceeded under mild conditions showing a broad substrate scope with diverse functional groups compatibility, which enabled a variety of novel seven-membered ferrocene fused azepines diastereoselectively. Further, a series of both kinetically and thermodynamically controlled diastereomers of the resultant ferrocene fused azepines containing point planar stereocenter has been prepared with excellent dr. The mechanistic understanding by DFT computations and control experiments suggested that at room temperature, the reductive elimination of σ-Rh bonded 8-membered rhodacyle having less steric hindrance between phenyl ring (downside) of allene and Cp* (upside) of Rh afforded kinetically controlled diastereomer having phenyl ring downside. The kinetically controlled diastereomer undergoes base mediated CH-allylic thermal isomerization leading to a thermodynamic stable diastereomer exclusively. We have also shown that novel seven-membered ferrocene fused azepines can be obtained enantioselectively (up to 90:10 er) by using Cramer's chiral $Cp^XRh(III)$ catalyst. Further, efforts are being made to diversify the enantioselective C-H bond in ferrocene using allenes coupling partner.

ASSOCIATED CONTENT

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

Experimental/methods; spectroscopic and characterization data (PDF)

Accession Codes

CCDC 2285354, 2285355, and 2285356 contain 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 CB21EZ, UK; fax: +441223336033.

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Notes

Authors declare no conflict of interest

ACKNOWLEDGMENT

S.K. thanks to SERB New Delhi (CRG/2019/000017) and IISER Bhopal for generous funding. R.A.T and D.P. acknowledge the Council of Scientific and Industrial Research New Delhi [09/1020(0113)/2017-EMR-I], SERB/CHM/2019, and UGC [14/(CSIR-UGC NET DEC 2019)] for fellowships, respectively. SK specially thanks to Dr. Sreenivas Katukojvala for his help in proposing the Rh-catalyzed [4+3] annulation reaction mechanism.

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