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, Diastereoselectivity, 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. Allenes are valuable synthons and well explored for [4+1] and [4+2] annulation but not yet explored for [4+3] annulation. 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 with >20:1 dr. Further, [4+3] annulation reaction in the presence of a chiral $RhCp^X$ catalyst (2.0 mol %) yielded chiral ferrocenyl azepines in 56% yield and up to 90:10 er. Mechanistic investigations by control experiments and isotopic labeling study 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 at room temperature. Under heating (60 ºC) conditions, kinetically controlled diastereomer undergo CH-allylic isomerization to afford completely thermodynamically controlled diastereomer, which has also been observed experimentally and computationally for isolated kinetically controlled diastereomer.

Introduction

Ferrocene, an organometallic sandwich complex, shows very good stability and redox properties.[1,2] In addition, disubstituted ferrocens possess quintessential planar chirality,[3] consequently, planar chiral ferrocenes are among the most explored examples that serve as excellent ligands in asymmetric catalysis.[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 (Figure 1).[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, respectively.[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 for heterocyclic fused ferrocenes, synthesis of these fused systems is difficult and requires intricate multistep synthetic protocols.[12]

Over the past few decades, many advances have been made in the field of transition metal (TM)-catalyzed asymmetric C-H functionalization to synthesize chiral ferrocenes[3, 13-16] over the conventional methods, namely enantioselective *ortho*-lithiation[17-22] and chiral resolution.[23-24] Consequently, a variety

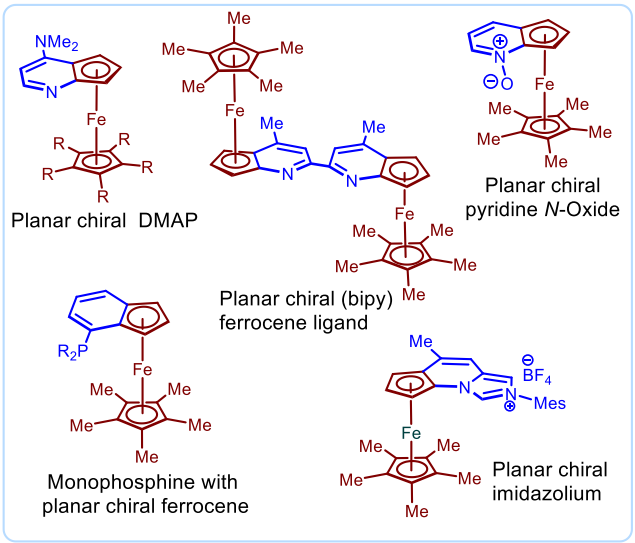
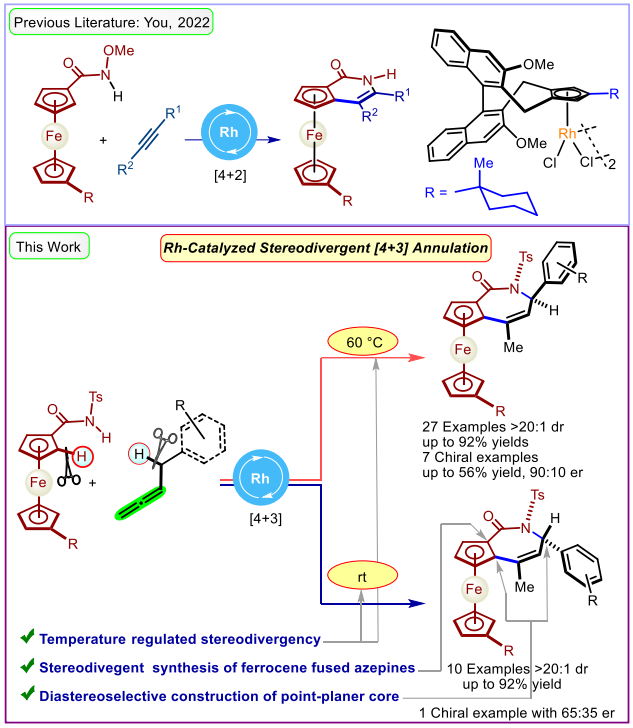


Figure 1. Depiction of Chiral Ferrocene Fused Heterocycles in Asymmetric Synthesis

of directing groups and coupling partners have been explored using chiral Rh,[25-28] Pd,[29-33] Ir,[34-35] Pt,[36] and Sc-based catalysis.[37] Although, TM-catalyzed intramolecular annulation reactions have been developed for the synthesis of planar chiral five or six-membered ferrocene-fused rings (Figure 1),

seven-membered ferrocene-fused heterocycles have not been reported. A seven-membered heterocyclic azepine core is present in various natural products, namely carbamazepine and darenzepine, mirtazapine, and oxcarbazepine, that are being used as drugs and agrochemicals.[38-39] Shibata *et al.*[36] have synthesized enantioselective intramolecular seven-membered planar chiral ferrocene fused azepines employing Pt-catalyzed cycloisomerization. The necessity of a designed pre-installed directing group limits the versatility of such approaches.[36, 40-43]

Scheme 1. Synthesis of Chiral Ferrocene Fused Heterocycle



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 achieve highly substituted complex chiral fused compounds in an efficient manner. Very recently, You and co-workers[44] constructed chiral fused ferrocene by using alkyne as a coupling partner in a [4+2] annulation reaction employing a chiral $RhCp^X$-catalyst (Scheme 1). The choice of coupling partner in direct C-H activation/annulation reactions influences the unique structural modifications in fused planar chiral ferrocenes. For example, allenes exhibit 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.[32, 45-47] These modulations, particularly [4+1][18], [4+2][19], and [3+3][48] type of annulations, are well-known in aromatic systems however, it is crucial to address the challenges related to regiocontrol in the reaction of allenes. Despite this, it provides the opportunity to introduce one more chiral center associated with the planar chirality in ferrocenes. However, simultaneously controlling planar and point chirality is difficult in diastereoselective manner and remains challenging.[49]

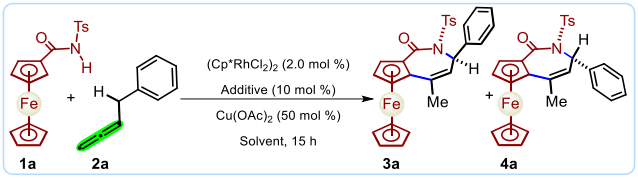
The synthesis of one of the diastereomers may be possible, however, the other corresponding complementary diastereomer is difficult. Consequently, the reaction becomes non-stereodivergent.[50-52] The stereodivergent pathways can yield multiple products having multiple stereocenters from the same starting material, whereas in diastereodivergence selective formation of two or more diastereomers is possible.[53-55]

Our group has studied the C-H activation in ferrocene for the construction of carbon-carbon and carbon-heteroatom (heteroatom = S/Se/Te) bonds.[56-62] Further, a variety of directing groups have been studied along with various coupling partners, namely alkanes, arenes, aryl halides, alkenes, and alkynes with ferrocenes by others and us.[44,54-60] However, allene substrates have not been used, which are known to undergo [4+1] and [4+2] annulation reactions affording five and six-membered rings, respectively. Herein, we report for the first time an Rh-catalyzed temperature-dependent stereodivegence synthesis of seven-membered ferrocene fused azepines by allene-driven [4+3] annulation. This protocol enables the synthesis of 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

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** (0.26 mmol), $(Cp^*RhCl_2)_2$ (2.0 mol %), additive (10 mol %), $Cu(OAc)_2$ (50 mol %), 2.0 mL solvent at 60 °C. [b] NaOPiv (1 equiv).[c] Isolated yield.

N-Tosylcarboxamide directing group (DG) was selected over earlier used bidentate *N*-8-aminoquinolinyl[60] and *N*-aryl/alkyl carboxamides DGs[60] 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.[63-65] However, it offers poor selectivity, presumably due to the ligand rigidity. Consequently, *N*-tosylferrocene carboxamide substrate **1a** was prepared from ferrocenyl chloride and *p*-tosylsulfonamide in ethyl acetate solvent (See SI 6). We started our investigation for Rh-catalyzed annulation with *N*-tosylferrocene carboxamide **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 led us to conduct a systematic solvent screening. 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[66] 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.[67] 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). After optimizing the conditions for both diastereomers **3a** and **4a**, we investigated the scope of the reaction with regard to different allenes **2a-2q** at 60 °C. Initially, in benzylallenes **2b**, *ortho*-methyl substitution provided a good yield of **3b** (70%) with an excellent dr >20:1. While allenes **2c** and **2d** 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 a phenyl ring with electron-donating groups (EDGs) provided moderate to good yields of **3g** (72%) and **3h** (75%).

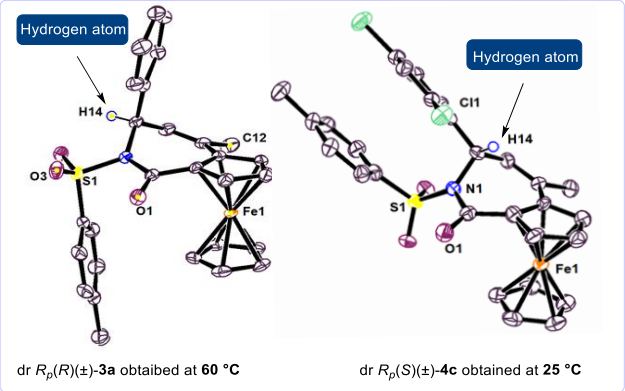
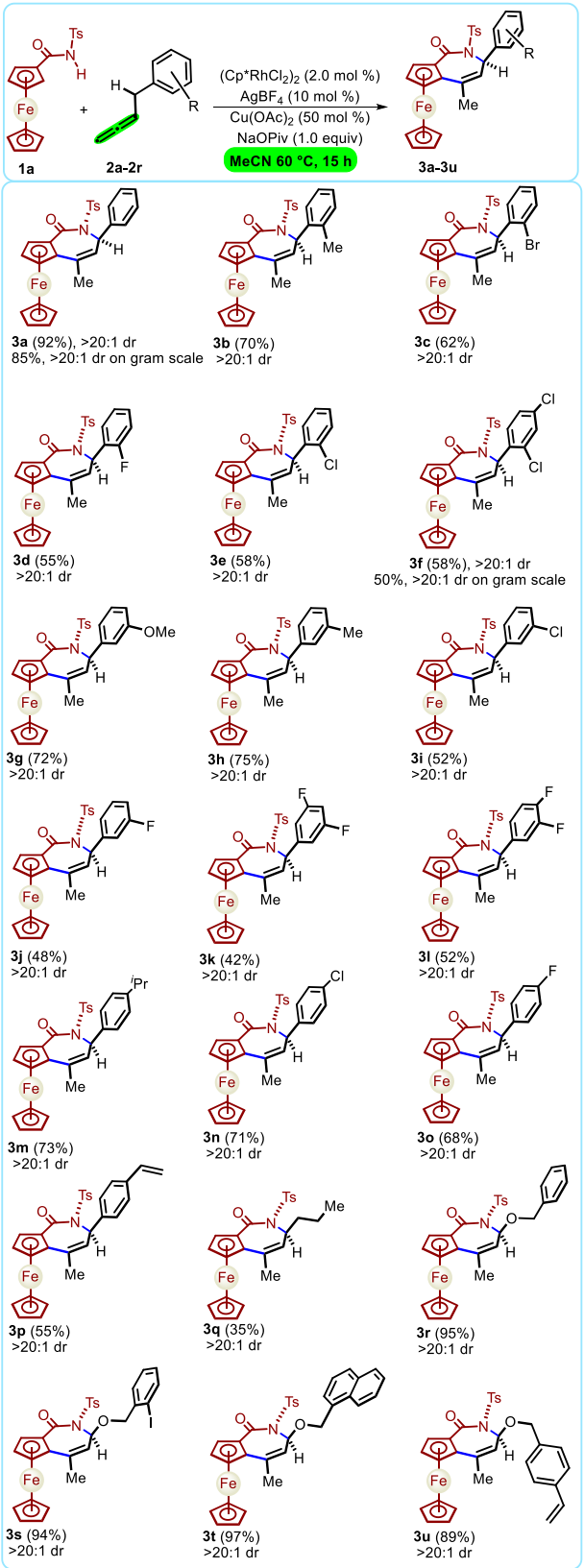


Figure 2. ORTEP Views of **3a** (CCDC: 2285354) and **4c (**CCDC: 2285355) with 50% Ellipsoid Probability. The phenyl ring (from allene) in **3a** is situated above side, and hydrogen is downside. In the diastereomer **4c** which is obtained at 25 °C, the phenyl ring of allene is downside, and hydrogen is up side. The rest of the hydrogen atoms are omitted for clarity.

Conversely, electron-withdrawing groups (EWGs) at *meta* position in phenyl allenes provided moderate yields (52-65%) of **3i-3l** with excellent dr (>20:1).

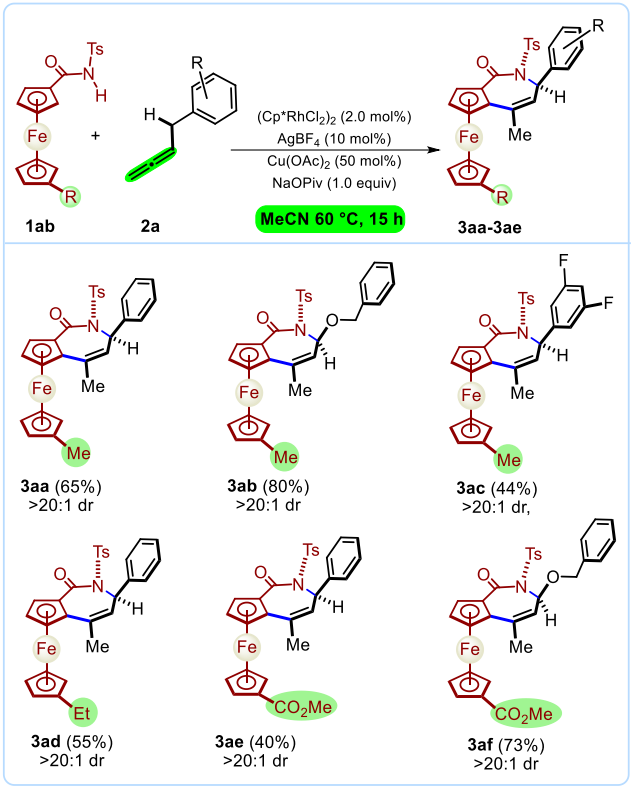
Moreover, the *para*-substituted allene **2k** with electron-donating ^{i}Pr and withdrawing fluoro and chloro substituents offered better yields (68-73%) of [4+3] annulated ferrocene fused azepines **3m-3o**. We also explored styrene-based allene **2m** substrate having alkene moiety under Rh-catalyzed [4+3] diastereoselective annulation reaction. To our delight, the reaction afforded the 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 more dominant than electronic factors. Next, aliphatic allene, a challenging substrate in Cp*M-catalyzed annulation,[68] 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 benzyloxyallenes (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*-tosylferrocene carboxamide having methyl and carboxymethyl on the second Cp ring were explored under the Rh-catalyzed reaction conditions (Scheme 3). Alkyl-substituted *N*-tosylferrocene carboxamides 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 2. Substrate Scope with regards to Allenes for the Synthesis of Thermodynamically Controlled Diastereomers[a]



[a] Reaction conditions: amide **1a** (0.13 mmol), allenes **2a-2r** (0.26 mmol), $(Cp^*RhCl_2)_2$ (2.0 mol %), $AgBF_4$ (10 mol %), $Cu(OAc)_2$ (50 mol %), NaOPiv (1.0 equiv), CH_3CN (2.0 mL) at 60°C.

Scheme 3. Substrate Scope with regards to Ferrocenecarboxamide[a]



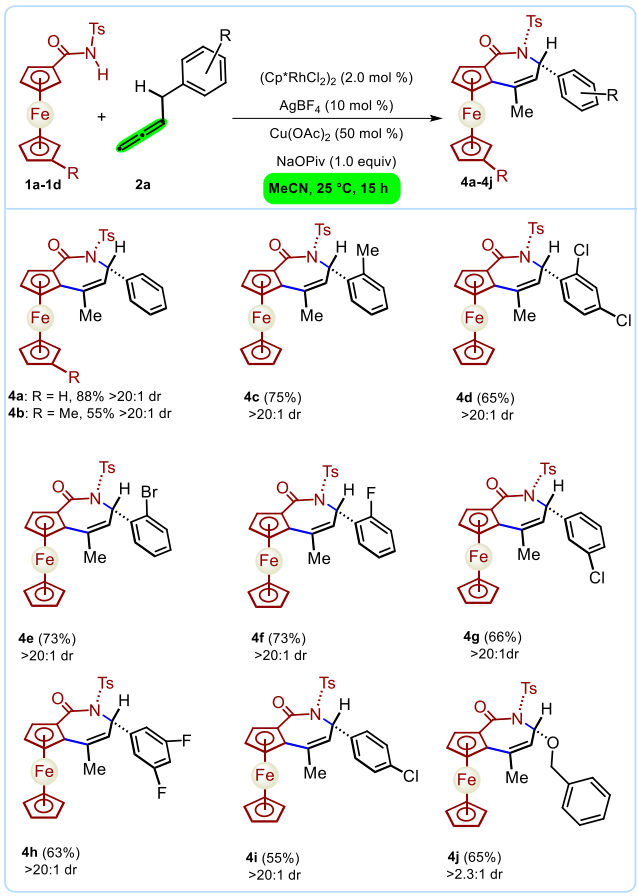
[a] Reaction conditions: amide **1ab** (0.13 mmol), **2a** (0.26 mmol), $(Cp^*RhCl_2)_2$ (2.0 mol %), $AgBF_4$ (10 mol %), $Cu(OAc)_2$ (50 mol %), NaOPiv (1.0 equiv) in CH_3CN (2.0 mL) at 60 °C.

It seems that the steric crowd on the second Cp ring slows down the reactivity as low yields (65% for **3aa** versus 92% for **3a** and 80% for **3ab** versus 95% of **3r**) were observed and slightly longer reaction hours are needed for the reaction.

To check the scalability, the developed reaction has been carried out at the gram scale for the preparation of diastereomers **3a** and **3f**. Indeed, nearly similar yields of 85 and 50% (*versus* 92 and 58%) with excellent dr were obtained for diastereomers **3a** and **3f**, respectively, suggesting the usefulness of the developed Rh-catalyzed [4+3] annulation reaction.

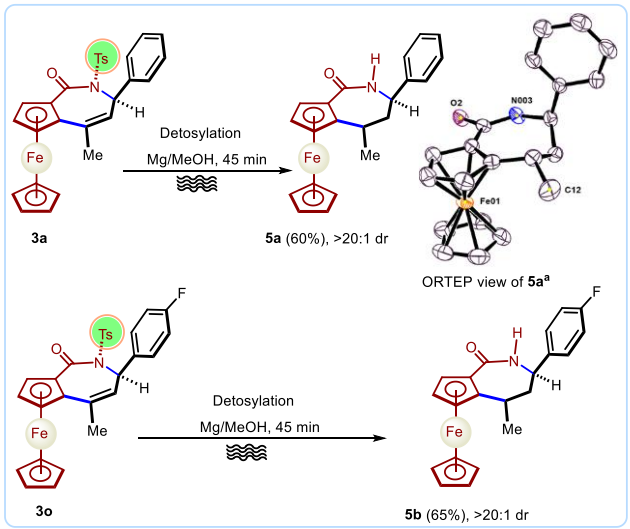
Next, the substrate scope was explored for the preparation of substituted kinetically controlled diastereomers at room temperature (Table 1, entry 10). Benzylallene **2a** afforded a good yield (88%) of kinetically controlled diastereomer **4a** with an excellent dr (>20:1), Scheme 4. Methyl substitution in the lower Cp ring of ferrocenecarboxamide **1b** led to a lower yield (55%) of the kinetically controlled [4+3] annulated diastereomer **4b**. Similarly, an electron-donating *ortho*-methyl substituent in phenyl allene **2b**, electron-withdrawing *ortho*-chloro, bromo, and fluoro and *meta*-chloro and *meta*-difluoro substituents in phenyl allenes **2c-2e** resulted in a slight decrease in the yields (75% and 55-66%) of annulated azepines **4c-4g**, however, with an excellent diastereomeric ratio. The lower yields of the substituted kinetically controlled diastereomers **4b-4g** may be due to the steric effect. Similarly, heteroatom-substituted benzyloxy allene **2p** led to a moderate yield (65%) of **4j**, and also reduced diastereomeric ratio (>2.3:1) was realized (Scheme 4).

Scheme 4. Substrate Scope for Kinetically Controlled Diastereomers



[a] Reaction conditions: Amide **1a** (0.13 mmol), allene **2a** (0.26 mmol), $(Cp^*RhCl_2)_2$ (2.0 mol %), $AgBF_4$ (10 mol %), $Cu(OAc)_2$ (50 mol %), NaOPiv (1.0 equiv), CH_3CN (2.0 mL) at 25°C.

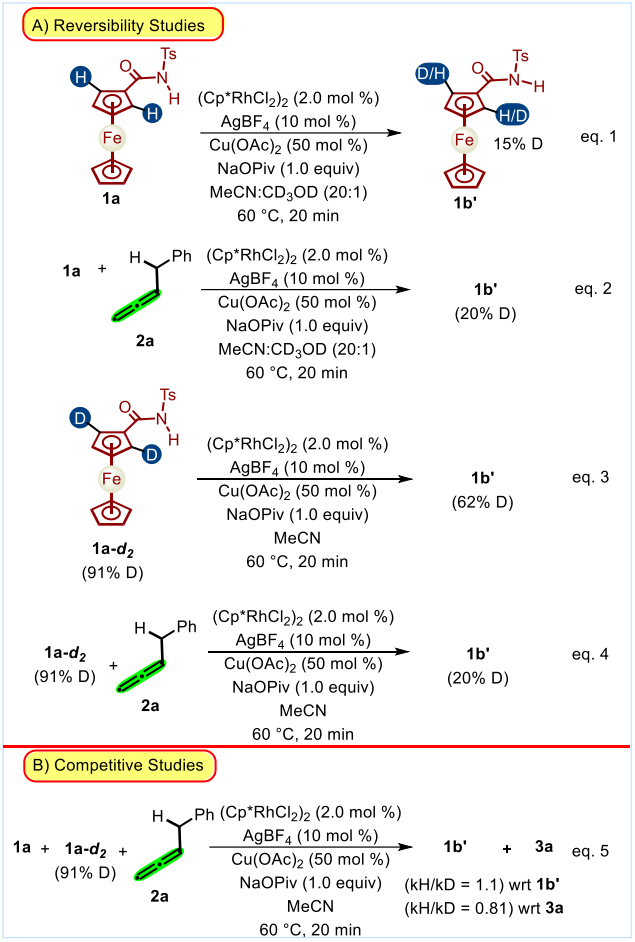
Scheme 5. Derivatization: Detosylation and Reduction of 3a and 3o for the Synthesis of Tetrahydro Azepine with intact *dr*.



[a] ORTEP View of **5a** with 50% Ellipsoid Probability, hydrogen atoms omitted for clarity. CCDC number = 2285356.

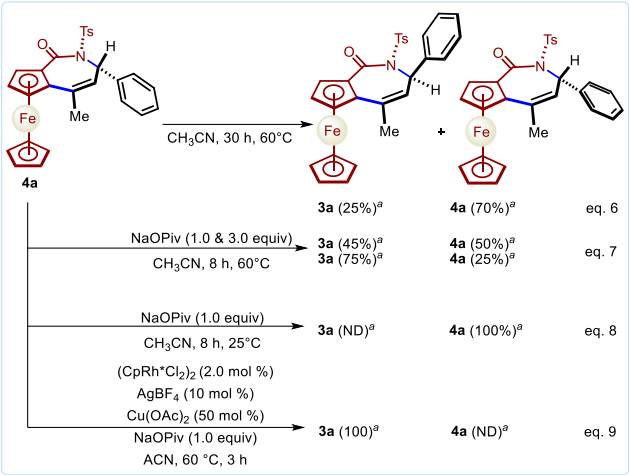
Further, seven-membered ferrocene fused azepines were modified by the removal of the *N*-tosyl group for a variety of late-stage transformations In our first attempt, the removal of the *N*-tosyl group by an established samarium iodide reagent[68] failed, and instead, cleavage of the *N*-tosyl group, a complex mixture, was observed. Alternatively, Mg in CH_3OH has been applied for the de-tosylation under sonication conditions.[69] To our delight, seven-membered ferrocene azepines **3a** and **3o** not only underwent detosylation but also led to the reduction of alkene in an unprecedented manner to afford N-H containing tetrahydro ferrocene fused azepines **5a** and **5b** in 60% and 65% yields with intact diastereoselectivity (>20:1) Scheme 5.

Scheme 6. Studies on Kinetic Isotope Effect



To check the reversibility of C–H metalation, the reaction was performed with deuterated methanol-d_4, which afforded deuteration at both the *ortho*-positions of *N*-tosyl ferrocenecarboxamide **1a** to give **1b'** (eq 1, Scheme 6). Similarly, the C-H metalation of *N*-tosyl ferroceneamide in the presence of CD_3OD and benzylallene coupling partner showed reversible deuteration (eq. 2, Scheme 6). Further, labeled *ortho* deuterated (91% deuteration) tosyl ferrocenecarboxamide **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, the C–H metalation of *N*-tosyl ferroceneamide **1a-*d*$_2$** in the presence of an benzylallene coupling partner showed the reversible deuteration in acetonitrile (eq. 4).

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



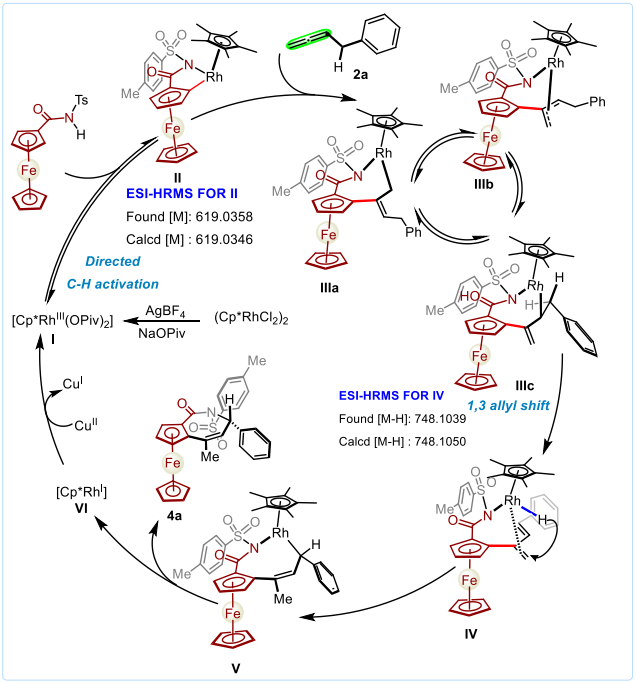
[a] NMR yield

To investigate whether the C–H metalation step was a rate-determining step, kinetic isotopic studies were carried out (eq. 5) found that a k_H/k_D value of 1.1 with respect to **1a** whereas isolated product **3a** suggested k_H/k_D value is 0.81 which indicate that C-H metalation is not rate determining step.

To gain more insights on to the temperature dependent diastereoselective construction of ferrocenyl azepines, control experiments have been carried out on isolated diastereomer **4a**, which was obtained at room temperature (eq. 6, Scheme 7). Diastereomer **4a**, upon heating alone in acetonitrile for 30 h, afforded only 25% conversion into thermodynamically controlled diastereomer **3a**. The heating of **4a** in the presence of NaOPiv (1 equiv), same equiv used under optimization reaction conditions) in CH_3CN afforded 45% conversion into **3a**, and in the presence of 3 equiv of NaOPiv, 75% conversion was realized (eq. 7). Whereas the same reaction at room temperature failed to provide any conversion of **4a** (eq. 8). The heating of the kinetically controlled diastereomer **4a** under the optimized reaction conditions in the presence of $(CpRh^*Cl_2)_2$ catalyst led to complete conversion into **3a** (eq. 9).

Based on the control experiments, isotopic labeling studies, and DFT computation (*vide infra*), a tentative mechanism is then proposed for Rh-catalyzed diastereodivergent synthesis of seven-membered ferrocene-fused azepines (Scheme 8). Initially, $[Cp^*Rh^{III}Cl_2]_2$ 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, the substitution of the acidic NH group of the substrate **1a** with OPiv ligand of $Cp^*Rh^{III}(OPiv)_2$ **I** would afford Rh-amidate type of intermediate, followed by the activation of C-H bond *via* concerted metalation deprotonation (CMD) could generate rhodacycle **II**. Further, the interaction of rhodacycle **II** with the benzylallene and subsequent migratory insertion of benzylallene into the Rh-C bond could generate σ-rhodium allylic species **IIIa**. This would transform into π-rhodium η^3-allylic rhodium **IIIb**, which may further isomerize to σ-rhodium allylic **IIIc** having Rh-C σ-bond adjacent to benzylic position.[69] The *in-situ* formation of rhodacycle **II** and intermediate **III** was also studied by mass spectrometry as observed masses for **II** and **III** were 619.0358 and 748.1039, respectively. *β*-H Elimination in **IIIC** led to the formation of

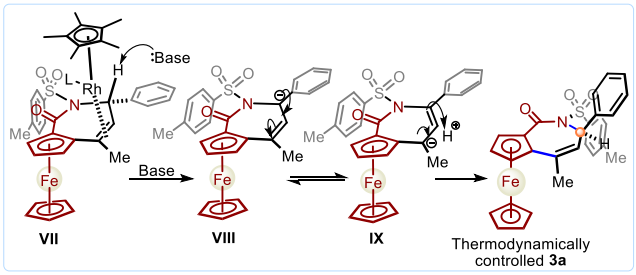
Scheme 8. Proposed Mechanism for Rh-Catalyzed [4+3] Annulation for the Formation of Kinetically Controlled Diastereomers[a]



[a] The mass values for intermediates **III** to **VI** are the same. The reaction mixture was subjected to mass analysis after 15 minutes of mixing of benzylallene with ferroceneamide **1a** under Rh-catalyzed reaction conditions.

rhodium hydride followed by a 1,3-allyl shift, which could afford η^2 π-alkene-Rh-hydride **IV**. Intramolecular hydride transfer to the terminal carbon of alkene provided a π-allyl-type Rh **IV** in an unprecedented manner. Next, π-allyl-type Rh **IV** may get converted into 8-membered σ-bonded rhodacycle **V**, 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.

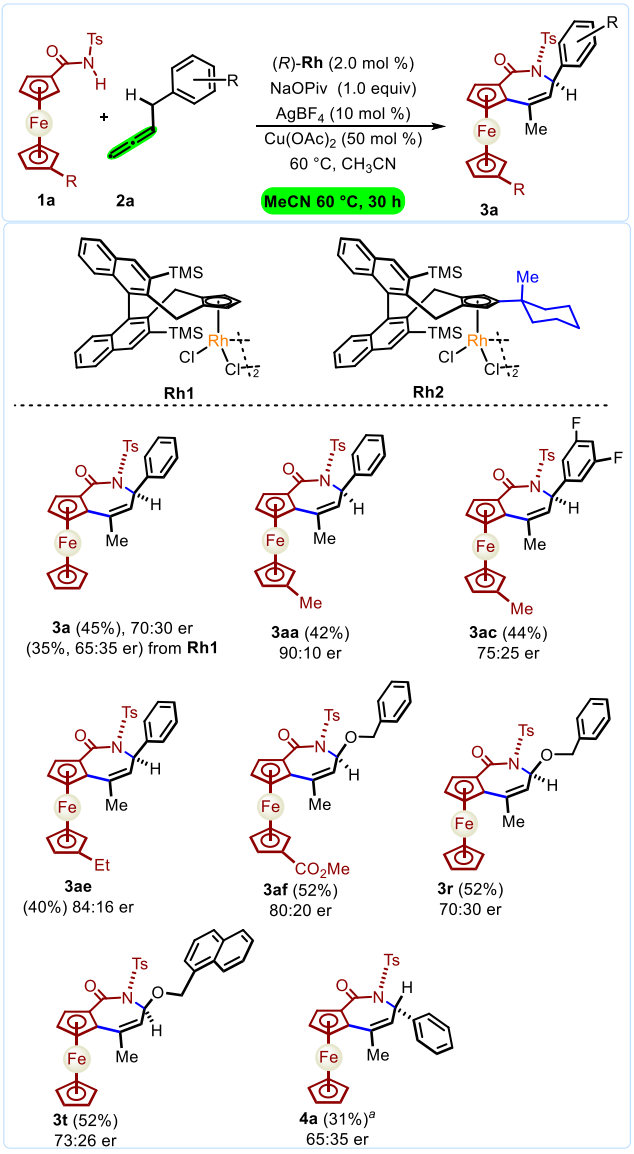
Scheme 9. Rh-Promoted and Base Mediated Thermal Isomerization of Kinetically Controlled **4a** into Thermodynamically Controlled **3a**.



The calculated energy difference between two diastereomers **3a** and **4a** is 5.2 kcal/mol using density functional thoery. The kinetic-controlled diastereomer **4a** could isomerize into the thermodynamic-controlled product **3a** *via* a Rh-promoted and base-mediated thermal isomerization (Scheme 9). Because NaOPiv or Rh-catalyst alone is not sufficient to isomerize **4a**

into **3a**, therefore, presence of both is necessary for the complete conversion (Scheme 7, *vide supra*). Initially, the π-coordination of the Rh-catalyst with **4a** could enhance the acidity of the allylic C-H bond *via* the formation of π-coordinated Rh **VII**. The removal of a proton from activated **VII** by the NaOPiv base leads to the formation of an allylic anion species **VIII**, which interconverts into **IX** by resonance. The allylic anion **IX** would accept a proton from the below side to lead the formation of the thermodynamic-controlled diastereomer **3a**. Insight about the conversion of kinetically controlled **4a** into thermodynamic distereomer **3a** was also obtained by DFT which showed that the allylic anionic intermediate **VIII** has the higher energies (35.55 and 40.75 kcal/mole) respectively (*see ESI, page S200*). The higher energy of anionic intermediate **VIII** suggests that the kinetically controlled diastereomer is relatively stable and high termal energy is required to convert into thermodaynamic product **3a**.

Scheme 10. Enantioselective [4+3] Annulation for the Construction of Chiral Ferrocene Fused Azepines[a]



[a] For **4a**, reaction was carried out at room temperature.

Isomerization of **4a** *via* Rh-hydride intermediate may not be possible because it could give back the hydride from the same face. It is worth noticing, except for the seven-membered ring azepine, the formation of five or six-membered isoindolinone or dihydroisoquinoline ring was not observed under the Rh-catalyzed reaction conditions. It is possibly due to the angle strain generated from the Cp-ring of ferrocene, which disfavors the six and seven-membered rhodacyclic intermediates.[70]

After the mechanistic understanding, we explored the enantioselective synthesis of seven-membered ferrocene fused azepines. It occurred that the enantioselective ring construction of seven-membered ring heterocycles, in general, and azepines, in particular, has not been studied despite myriad enantioselective studies on five and six-membered ring construction.[17-19] 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 Rh,[69, 71-72] Co,[73] and Ir-catalysts[74-75] with Cp^X ligands and have been applied in various asymmetric synthetic methodologies. We have prepared a trimethyl silyl substituted back wall containing cyclopentadienyl chiral catalyst **Rh1**.[76] 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 under the optimized reaction conditions, which resulted in the formation of seven-membered ferrocene azepine **3a** in a yield of 35% and an enantioselectivity of 60:40 er. **Rh2** 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 benzylallene under **Rh2**-catalyzed [4+3] annulation afforded chiral kinetically controlled diastereomer **4a** with 65:35 er and 31% yield (Scheme 10).

Based on a literature survey,[44] 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 ferrocenecarboxamides **1b-1d** and subjected them to the **Rh2**-catalyzed optimized reaction conditions. 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.

Conclusion

In conclusion, we have developed a RhCp* catalyzed temperature-controlled stereodivergent regioselective intermolecular [4+3] annulation of *N*-tosylferrocenecarboxamide with allenes. The developed C–H and C-N annulation reaction proceeded under mild conditions, showing a broad substrate scope with diverse functional group compatibility, which enabled a variety of novel seven-membered ferrocene fused azepines. 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 synthesized ferrocene fused azepines have been reduced further, and the tosyl group has been deprotected into the N-H group for late-stage transformation. The mechanistic

understanding suggested that at room temperature, the reductive elimination of σ-Rh bonded 8-membered rhodacyle having less steric hindrance between phenyl ring on (downside) of allene and Cp* (upside) of Rh afforded kinetically controlled diastereomer having phenyl ring downside. The kinetically controlled diastereomer undergoes Rh-promoted and base-mediated CH-allylic thermal isomerization, leading to a thermodynamic stable diastereomer exclusively and confirmed by DFT analysis. We have also shown that the novel seven-membered ferrocene fused azepines can be obtained enantioselectively (up to 90:10 er) by using Cramer's chiral $Cp^XRh(III)$ type catalyst. The developed reaction provides access to seven-membered heterocycles from allenes for the first time. Currently, efforts are being made to diversify the enantioselective C–H bond in arenes using an 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
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ACKNOWLEDGMENT

S.K. thanks to SERB New Delhi (CRG/2019/000017) and IISER Bhopal for generous funding. R.A.T., D.P. and S.J. acknowledge the Council of Scientific and Industrial Research New Delhi [09/1020(0113)/2017-EMR-I], SERB/CHM/2019, UGC [14/(CSIR-UGC NET DEC 2019)], and UGC [14/(CSIR-UGC NET JUNE 2017)] for fellowships, respectively. S.K. thanks to Mr. Vikram Singh for synthesizing allenes and ferrocene azepines derivatives. SK specially thanks to Dr. Sreenivas Katukojvala for his help in proposing the Rh-catalyzed [4+3] annulation reaction mechanism and proof reading the manuscript. R.A.T. thanks to Mr. Suman Sar and Mr. Sachin S. Gorad for helpful discussion on diastereodivergent concept.

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SYNOPSIS TOC: